Research Advances on the Microbiota-Gut-Brain Axis in Epilepsy: A Postprint

Authors: Li Jing, Liu Ziqi, Qian Li, Yao Ruiqin, Qian Li, Yao Ruiqin

Date: 2025-02-24T00:00:00+00:00

Abstract

Epilepsy is a chronic neurological disorder characterized by recurrent and unprovoked seizures, affecting more than 50 million people worldwide, with nearly 30% of patients remaining uncontrolled by medication. Notably, individuals with inflammatory bowel disease exhibit a higher susceptibility to epilepsy. The gut-brain axis denotes the bidirectional communication between the intestine and brain, regulating intestinal homeostasis and the central nervous system via neural networks and neuroendocrine, immune, and inflammatory pathways. Recent studies have demonstrated that intestinal dysfunction and dysbiosis may be implicated in the pathogenesis and susceptibility to epilepsy. Moreover, strategies aimed at restoring the gut microbiota, including fecal microbiota transplantation, probiotic intervention, and ketogenic diet, have shown promising therapeutic effects in refractory epilepsy, further substantiating the potential link between gut microbiota and epilepsy. This review introduces the microbiota-gut-brain axis and synthesizes the established roles of gut microbiota in epilepsy pathogenesis and treatment from previous research, providing a reference for exploring novel microbiota-based therapeutic approaches for epilepsy.

Full Text

Preamble

Review and Monograph
Research Progress on the Role of the Microbiota-Gut-Brain Axis in Epilepsy

LI Jing[1,2], LIU Ziqi[3,4], QIAN Li[3,4], *YAO Ruiqin*[1,2]

[1]Xuzhou Medical University, Xuzhou 221004, China
[2]Xuzhou Key Laboratory of Neurobiology, Xuzhou 221004, China
[3]Yangzhou University, Yangzhou 225001, China

[4]Key Laboratory of Jiangsu Province University for Nucleic Acid & Cell Fate Manipulation, Yangzhou 225001, China

Corresponding authors: QIAN Li, Professor; E-mail: qianl@yzu.edu.cn
YAO Ruiqin, Professor; E-mail: wenxi_{yao}@163.com

Abstract Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures, affecting over 50 million people worldwide, with nearly 30% of patients unable to achieve seizure control through medication. Notably, individuals with inflammatory bowel disease are at higher risk of developing epilepsy. The gut-brain axis refers to bidirectional communication between the gut and brain that regulates intestinal homeostasis and central nervous system function through neural networks, neuroendocrine, immune, and inflammatory pathways. Recent studies suggest that gut dysfunction and dysbiosis may play a role in the pathogenesis and susceptibility of epilepsy. Additionally, interventions such as fecal microbiota transplantation, probiotic therapy, and ketogenic diets, which aim to restore gut microbiota balance, have shown promising effects in treating refractory epilepsy, further supporting a potential link between gut microbiota and epilepsy. This review synthesizes current knowledge on the role of gut microbiota in epilepsy pathogenesis and treatment, exploring potential microbiota-based therapeutic options.

[**Keywords**] Epilepsy; Microbiota-gut-brain axis; Gut microbiota; Review

Funding: Jiangsu Province Graduate Research Innovation Program (KYCX22_{2869})

Citation: LI J, LIU Z Q, QIAN L, et al. Research progress on the role of the microbiota-gut-brain axis in epilepsy [J]. Chinese General Practice, 2025. DOI: 10.12114/j.issn.1007-9572.2025.0003. [Epub ahead of print] [www.chinagp.net]

1. Literature Search Strategy

We conducted computerized searches of PubMed, Web of Science, and other databases from inception to December 2024. Chinese search terms included “epilepsy,”“gut microbiota,”“intestinal microbes,”and “microbiota-gut-brain axis.” English search terms included “epilepsy,” “Microbiome-gut-brain axis,” “FMT,” and “Gut.” Inclusion criteria: literature addressing the role of the microbiota-gut-brain axis in epilepsy and the neurobiological mechanisms of epileptogenesis. Exclusion criteria: irrelevant content, poor quality, or inability to obtain full text. A total of 68 articles were ultimately included.

2. Microbiota-Gut-rain Axis

The gut microbiota comprises diverse microorganisms, including bacteria from 50 phyla, with total numbers exceeding human somatic and germ cells by a factor of 10. A robust gut microbiota is characterized by dynamic equilibrium and diversity, with six dominant phyla (Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia), among which Firmicutes and Bacteroidetes account for approximately 90% of the composition. The trillions of microbes in the gut serve as key regulators of the gut-brain axis. For example, gut microbiota can control gastrointestinal function by modulating the enteric nervous system and synthesize various neurotransmitters including serotonin and γ-aminobutyric acid (GABA) to participate in behavioral and cognitive activities. In diseases affecting the brain and behavior such as Parkinson' s disease, reduced levels of short-chain fatty acids (microbial metabolites) have been observed in feces. Overall, the gut-brain axis in neurological disorders represents a system that can positively or negatively influence brain function through microbiota activity, functioning like a dynamic bidirectional neuroendocrine system encompassing direct neural connections, immune factors, and endocrine signals.

---

3. Alterations of Gut Microbiota in Epilepsy Patients

Epilepsy patients, particularly those with refractory epilepsy, typically exhibit gut microbiota compositions distinct from healthy controls. For instance, studies have found that refractory epilepsy patients show lower relative abundances of Bacteroidetes and Proteobacteria but higher abundances of Firmicutes and Actinobacteria. Another study reported increased numbers of Proteobacteria in epilepsy patients compared with healthy subjects. Gut microbiota (GM) dysbiosis and seizure frequency may be two closely related core features of epilepsy. Research in rodent epilepsy models has observed that animals are more susceptible to seizures under stressful conditions, and stress can alter gut microbiota. These findings demonstrate an apparent association between gut microbiota composition and susceptibility to epileptic activity.

---

4. Possible Mechanisms of the Microbiota-Gut-Brain Axis in Epilepsy

The therapeutic effects of microbiota modulation and its potential as a biomarker remain incompletely understood. This section summarizes recent research progress based on the microbiota-gut-brain axis and explores therapeutic strategies for epilepsy.

4.1 Immune and Inflammatory Pathways

The pathogenesis of epilepsy is associated with neuroimmunity and neuroinflammation. Astrocytes perform multiple functions including regulating blood-cerebrospinal fluid barrier integrity, neurotransmitter cycling, and immune responses. Microglia mediate innate immune reactions. Both microglia and astrocytes participate in epileptogenesis by releasing excessive cytokines. For example, gut microbes metabolize dietary tryptophan into aryl hydrocarbon receptor agonists that interact with their receptors to control microglial activation and transformation, regulating expression of transforming growth factor α (TGF-α) and vascular endothelial growth factor β (VEGF-β), thereby modulating pathogenic astrocyte activity. Additionally, epilepsy pathogenesis involves invasion of brain tissue by peripheral immune cells such as T cells and monocytes. When gut microbiota dysbiosis occurs, the intestinal immune barrier is compromised, allowing bacteria and their metabolites such as cytokines and peptidoglycans to enter circulation, activate peripheral immune cells, alter blood-cerebrospinal fluid barrier permeability, and ultimately trigger central nervous system inflammatory responses. This immune reaction may directly or indirectly induce epilepsy. While these findings suggest that gut microbiota influences epilepsy occurrence through immune-inflammatory pathways, definitive mechanisms require further investigation.

4.2 Neural Pathways

The microbiota-gut-brain axis exerts regulatory effects through interconnected neural systems. The most important signal transmission pathway between the enteric nervous system (ENS) and central nervous system (CNS) is the vagus nerve. Through neuropods utilizing glutamate as a neurotransmitter to synapse with vagal afferents, gut signals can be transmitted to brainstem sensory nuclei, forming a gut-brain neural circuit. An oral inoculation mouse model with *Campylobacter jejuni* induced c-fos expression in sensory ganglia and primary brainstem vagal sensory relay nuclei, demonstrating that intestinal stimulation can modulate brain activity through the autonomic nervous system. Vagus nerve stimulation has long been used as a standard epilepsy treatment, with studies reporting that electrical stimulation of vagal afferent fibers can alter concentrations of serotonin, GABA, and glutamate in the brain, thereby explaining its role in epilepsy. In summary, the microbiota-gut-brain axis plays an important role in epilepsy initiation, propagation, and control through multilevel neural regulatory mechanisms that coordinate gut-brain signal transmission and neurotransmitter balance.

4.3 Endocrine Signaling and Gut Microbiota Metabolite Pathways

Neurotransmitter imbalance is closely associated with epileptogenesis. Gut microbes can directly secrete neurotransmitters or stimulate gastrointestinal cells to produce them via metabolites. Different gut microbes produce different neurotransmitters: for example, *Enterococcus*, *Streptococcus*, and *E. coli* can produce

serotonin; *Lactobacillus* and *Bifidobacterium* can produce GABA; and *E. coli* and *Bacillus* can produce norepinephrine (NE) and dopamine. Epileptic foci exhibit neurotransmitter imbalances such as low GABA activity, high glutamate activity, high dopamine and NE activity, and low serotonin activity. In germ-free (GF) mice, plasma tryptophan concentrations are 40% higher than in conventional mice, while conventional mice show 280% higher plasma serotonin concentrations than GF mice, indicating that gut microbiota plays a crucial role in converting peripheral tryptophan to serotonin. Moreover, *Clostridium* in GF mice can promote intestinal 5-hydroxytryptamine (5-HT) biosynthesis by upregulating colonic tryptophan hydroxylase 1 (the rate-limiting enzyme in serotonin synthesis). Temporal lobe epilepsy patients exhibit 5-HT deficiency, and drug combinations that increase 5-HT, such as selective serotonin reuptake inhibitors, may improve seizure control.

Short-chain fatty acids (SCFAs) are microbial metabolites and a current research hotspot in the microbiota-gut-brain axis, mainly including acetate, propionate, and butyrate. SCFAs regulate epileptogenesis through direct or indirect pathways in microglia, modulating the gut-brain neural system, blood-cerebrospinal fluid barrier permeability, and stress response functions. For example, sodium butyrate can improve mitochondrial dysfunction and protect brain tissue from oxidative stress and neuronal apoptosis through the Keap1/Nrf2/HO-1 pathway, thereby increasing seizure threshold and reducing seizure intensity. Studies in pentylenetetrazol (PTZ)-induced epileptic mouse models have further investigated the protective effects and mechanisms of different SCFAs against epilepsy.

---

5. Therapeutic Interventions

5.1 Probiotics

Probiotics have been shown to reduce seizure frequency and severity by altering gut microbiota composition. One study found that probiotic administration with *Lactobacillus casei* to newborns with rotavirus infection reduced epilepsy risk by 10-fold compared to untreated infected controls. Another study reported that 45 patients with refractory epilepsy treated with a multi-strain probiotic containing *Lactobacillus acidophilus*, *Lactobacillus plantarum*, and *Lactobacillus casei* showed increased GABA levels, reduced inflammatory interleukin-6 (IL-6), and over 50% seizure reduction in 28.9% of patients. Animal studies further demonstrated that probiotic supplementation not only alleviates seizures but also improves epilepsy-induced cognitive impairment and hippocampal long-term potentiation. Although the exact mechanisms linking probiotic therapy and epilepsy remain unclear, probiotics may serve as an adjunctive treatment for epilepsy patients due to their safety profile and clinical outcomes.

5.2 Fecal Microbiota Transplantation (FMT)

FMT has proven effective for treating epilepsy by reconstructing gut microbiota. One study reported a patient with both Crohn' s disease and refractory epilepsy who achieved complete seizure control and significant reduction in Crohn' s disease activity index after FMT treatment, with prevention of post-medication seizure recurrence. Animal studies indicate that FMT can significantly improve epilepsy control by altering gut microbiota composition. In epileptic mice treated with FMT, intestinal glial cell activation was reduced, inflammatory cytokine production decreased, and intestinal barrier function improved, demonstrating that FMT provides neuroprotective anti-epileptic effects by modifying gut microbiota. However, FMT application still faces challenges, including potential bacterial and viral transmission risks and possible disruption of microbiota diversity leading to increased antibiotic resistance.

5.3 Dietary Intervention

Dietary intervention, particularly the ketogenic diet, has proven effective and promising for epilepsy treatment. Since 1921, the ketogenic diet—characterized by a unique high-fat, low-carbohydrate, and adequate-protein ratio—has been widely used for refractory epilepsy. The classic ketogenic diet ratio of 4:1 (fat to protein plus carbohydrates) exerts multiple anti-epileptic mechanisms by modulating neurotransmitters, brain energy metabolism, oxidative stress, ion channels, and GM composition. The ketogenic diet benefits over one-third of epilepsy patients and has proven effective for treating childhood refractory epilepsy. Studies show that the ketogenic diet reduces harmful bacteria such as *Salmonella*, *Escherichia*, and *Vibrio* in Enterobacteriaceae while increasing *Prevotella* and *Bacteroides*, producing abundant short-chain fatty acids and reducing seizure frequency by 50% in 64% of children. The β-hydroxybutyric acid (BHB) produced by the ketogenic diet can increase brain GABA and the GABA/glutamate ratio to inhibit epilepsy. However, the specific effects of the ketogenic diet on gut microbiota remain under investigation, with some studies suggesting potential negative effects such as reduced *Bifidobacterium* and increased *E. coli*.

---

6. Summary and Outlook

This review summarizes current evidence regarding the microbiota-gut-brain axis and its potential roles in epilepsy pathogenesis, prevention, and treatment. Numerous studies indicate that intestinal dysfunction and dysbiosis are closely associated with epilepsy onset and susceptibility, with specific gut microbes serving as potential biomarkers and therapeutic targets for refractory epilepsy, though the underlying mechanisms remain incompletely understood. Additionally, probiotics, FMT, and ketogenic diets significantly influence gut microbiota and further affect seizure frequency and severity. These interventions may play

important roles in improving epilepsy symptoms by modulating gut microbiota composition.

Despite preliminary achievements in understanding the microbiota-gut-brain axis in epilepsy, research on the brain-gut axis relationship remains in its early stages, requiring cautious interpretation of existing and future findings. On one hand, larger, well-designed studies are needed to clarify the pathways and mechanisms of the microbiota-gut-brain axis in epilepsy. On the other hand, previous studies lack consensus on which specific gut microbes are closely associated with epilepsy, likely due to multiple factors including patient age, epilepsy etiology, dietary patterns, geographic location, and socioeconomic status. Therefore, while dietary interventions or probiotic therapy represent promising approaches, current research remains limited in characterizing gut microbial components. Future research on the microbiota-gut-brain axis will become an important direction in epilepsy studies and holds promise as a novel diagnostic and therapeutic target for refractory epilepsy associated with the gut-brain axis.

References

[1] BEGHI E, GIUSSANI G, SANDER J W. The natural history and prognosis of epilepsy[J]. Epileptic Disord, 2015, 17(3): 243-253. DOI: 10.1684/epd.2015.0751.
[2] BEGHI E. The epidemiology of epilepsy[J]. Neuroepidemiology, 2020, 54(2): 185-191. DOI: 10.1159/000503831.
[3] GOLUB V M, REDDY D S. Post-traumatic epilepsy and comorbidities: advanced models, molecular mechanisms, biomarkers, and novel therapeutic strategies[J]. Pharmacol Rev, 2022, 74(2): 387-438. DOI: 10.1124/pharmrev.121.000375.
[4] JR E J. The current place of epilepsy surgery[J]. Curr Opin Neurol, 2018, 31(2): 192-197. DOI: 10.1097/WCO.0000000000000528.
[5] SHENG J Y, LIU S, QIN H J, et al. Drug-resistant epilepsy and surgery[J]. Curr Neuropharmacol, 2018, 16(1): 17-28. DOI: 10.2174/1570159X15666170504123316.
[6] DE CARO C, LEO A, NESCI V, et al. Intestinal inflammation increases convulsant activity and reduces antiepileptic drug efficacy in a mouse model of epilepsy[J]. Sci Rep, 2019, 9(1): 13983. DOI: 10.1038/s41598-019-50542-0.
[7] LÓPEZ GONZÁLEZ F J, RODRÍGUEZ OSORIO X, GIL-NAGEL REIN A, et al. Drug-resistant epilepsy: definition and treatment alternatives[J]. Neurologia, 2015, 30(7): 439-446. DOI: 10.1016/j.nrl.2014.04.012.
[8] GONG X, LIU X, CHEN C, et al. Alteration of gut microbiota in patients with epilepsy and the potential index as a biomarker[J]. Front Microbiol, 2020, 11: 517797. DOI: 10.3389/fmicb.2020.517797.
[9] ŞAFAK B, ALTUNAN B, TOPÇU B, et al. The gut microbiome in epilepsy[J]. Microb Pathog, 2020, 139: 103853. DOI: 10.1016/j.micpath.2019.103853.
[10] PENG A J, QIU X M, LAI W L, et al. Altered composition of the gut microbiome in patients with drug-resistant epilepsy[J]. Epilepsy Res, 2018, 147:

1-7. DOI: 10.1016/j.eplepsyres.2018.09.013.
[11] CITRARO R, LEMBO F, DE CARO C, et al. First evidence of altered microbiota and intestinal damage and their link to absence epilepsy in a genetic animal model, the WAG/Rij rat[J]. Epilepsia, 2021, 62(2): 529-541. DOI: 10.1111/epi.16813.
[12] MAYER E A, KNIGHT R, MAZMANIAN S K, et al. Gut microbes and the brain: paradigm shift in neuroscience[J]. J Neurosci, 2014, 34(46): 15490-15496. DOI: 10.1523/JNEUROSCI.3299-14.2014.
[13] CLAUDINO DOS SANTOS J C, OLIVEIRA L F, NOLETO F M, et al. Gut-microbiome-brain axis: the crosstalk between the vagus nerve, alpha-synuclein and the brain in Parkinson' s disease[J]. Neural Regen Res, 2023, 18(12): 2611-2614. DOI: 10.4103/1673-5374.373673.
[14] BASIJI K, SENDANI A A, GHAVAMI S B, et al. The critical role of gut-brain axis microbiome in mental disorders[J]. Metab Brain Dis, 2023, 38(8): 2547-2561. DOI: 10.1007/s11011-023-01248-w.
[15] IANNONE L F, PREDA A, BLOTTIÈRE H M, et al. Microbiota-gut brain axis involvement in neuropsychiatric disorders[J]. Expert Rev Neurother, 2019, 19(10): 1037-1050. DOI: 10.1080/14737175.2019.1638763.
[16] QUIGLEY E M M. Microbiota-brain-gut axis and neurodegenerative diseases[J]. Curr Neurol Neurosci Rep, 2017, 17(12): 94. DOI: 10.1007/s11910-017-0802-6.
[17] ADAK A, KHAN M R. An insight into gut microbiota and its functionalities[J]. Cell Mol Life Sci, 2019, 76(3): 473-493. DOI: 10.1007/s00018-018-2943-4.
[18] BÄCKHED F, ROSWALL J, PENG Y Q, et al. Dynamics and stabilization of the human gut microbiome during the first year of life[J]. Cell Host Microbe, 2015, 17(5): 690-703. DOI: 10.1016/j.chom.2015.04.004.
[19] RINNINELLA E, RAOUL P, CINTONI M, et al. What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet, and diseases[J]. Microorganisms, 2019, 7(1): 14. DOI: 10.3390/microorganisms7010014.
[20] YAMASHIRO Y. Gut microbiota in health and disease[J]. Ann Nutr Metab, 2017, 71(3-4): 242-246. DOI: 10.1159/000481627.
[21] CARABOTTI M, SCIROCCO A, MASELLI M A, et al. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems[J]. Ann Gastroenterol, 2015, 28(2): 203-209.
[22] WANG H X, WANG Y P. Gut Microbiota-brain Axis[J]. Chin Med J (Engl), 2016, 129(19): 2373-2380.
[23] SILVA Y P, BERNARDI A, FROZZA R L. The role of short-chain fatty acids from gut microbiota in gut-brain communication[J]. Front Endocrinol, 2020, 11: 25. DOI: 10.3389/fendo.2020.00025.
[24] GAREAU M G. Microbiota-gut-brain axis and cognitive function[J]. Adv Exp Med Biol, 2014, 817: 357-371. DOI: 10.1007/978-1-4939-0897-4_{16}.
[25] DINAN T G, CRYAN J F. The microbiome-gut-brain axis in health and disease[J]. Gastroenterol Clin North Am, 2017, 46(1): 77-89. DOI: 10.1016/j.gtc.2016.09.007.
[26] LINDEFELDT M, ENG A, DARBAN H, et al. The ketogenic diet

influences taxonomic and functional composition of the gut microbiota in children with severe epilepsy[J]. NPJ Biofilms Microbiomes, 2019, 5(1): 5. DOI: 10.1038/s41522-018-0073-2.
[27] LUM G R, OLSON C A, HSIAO E Y. Emerging roles for the intestinal microbiome in epilepsy[J]. Neurobiol Dis, 2020, 135: 104576. DOI: 10.1016/j.nbd.2019.104576.
[28] MOLINA-TORRES G, RODRIGUEZ-ARRASTIA M, ROMAN P, et al. Stress and the gut microbiota-brain axis[J]. Behav Pharmacol, 2019, 30(2 and 3-Spec Issue): 187-200. DOI: 10.1097/FBP.0000000000000478.
[29] YAMANAKA G, MORICHI S, TAKAMATSU T, et al. Links between immune cells from the periphery and the brain in the pathogenesis of epilepsy: a narrative review[J]. Int J Mol Sci, 2021, 22(9): 4395. DOI: 10.3390/ijms22094395.
[30] KHAKH B S, SOFRONIEW M V. Diversity of astrocyte functions and phenotypes in neural circuits[J]. Nat Neurosci, 2015, 18(7): 942-952. DOI: 10.1038/nn.4043.
[31] GINHOUX F, LIM S, HOEFFEL G, et al. Origin and differentiation of microglia[J]. Front Cell Neurosci, 2013, 7: 45. DOI: 10.3389/fncel.2013.00045.
[32] DING X M, ZHOU J, ZHAO L, et al. Intestinal flora composition determines microglia activation and improves epileptic episode progress[J]. Front Cell Infect Microbiol, 2022, 12: 835217. DOI: 10.3389/fcimb.2022.835217.
[33] ROTHHAMMER V, BORUCKI D M, TJON E C, et al. Microglial control of astrocytes in response to microbial metabolites[J]. Nature, 2018, 557(7707): 724-728. DOI: 10.1038/s41586-018-0119-x.
[34] DJUKIC M, MILDNER A, SCHMIDT H, et al. Circulating monocytes engraft in the brain, differentiate into microglia and contribute to the pathology following meningitis in mice[J]. Brain, 2006, 129(Pt 9): 2394-2403. DOI: 10.1093/brain/awl206.
[35] MORADI K, ASHRAF-GANJOUEI A, TAVOLINEJAD H, et al. The interplay between gut microbiota and autism spectrum disorders: a focus on immunological pathways[J]. Prog Neuropsychopharmacol Biol Psychiatry, 2021, 106: 110091. DOI: 10.1016/j.pnpbp.2020.110091.
[36] GAMAN A, KUO B. Neuromodulatory processes of the brain-gut axis[J]. Neuromodulation, 2008, 11(4): 249-259. DOI: 10.1111/j.1525-1403.2008.00172.x.
[37] KAELBERER M M, BUCHANAN K L, KLEIN M E, et al. A gut-brain neural circuit for nutrient sensory transduction[J]. Science, 2018, 361(6408): eaat5236. DOI: 10.1126/science.aat5236.
[38] GOEHLER L E, GAYKEMA R P A, OPITZ N, et al. Activation in vagal afferents and central autonomic pathways: early responses to intestinal infection with *Campylobacter jejuni*[J]. Brain Behav Immun, 2005, 19(4): 334-344. DOI: 10.1016/j.bbi.2004.09.002.
[39] ATTENELLO F, AMAR A P, LIU C, et al. Theoretical basis of vagus nerve stimulation[J]. Prog Neurol Surg, 2015, 29: 20-28. DOI: 10.1159/000434652.
[40] RESSLER K J, MAYBERG H S. Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic[J]. Nat Neurosci,

2007, 10(9): 1116-1124. DOI: 10.1038/nn1944.
[41] WERNER F M, COVEÑAS R. Classical neurotransmitters and neuropeptides involved in generalized epilepsy in a multi-neurotransmitter system: How to improve the antiepileptic effect?[J]. Epilepsy Behav, 2017, 71(Pt B): 124-129. DOI: 10.1016/j.yebeh.2015.01.038.
[42] BARRETT E, ROSS R P, O' TOOLE P W, et al. γ-Aminobutyric acid production by culturable bacteria from the human intestine[J]. J Appl Microbiol, 2012, 113(2): 411-417. DOI: 10.1111/j.1365-2672.2012.05344.x.
[43] DINAN T G, STILLING R M, STANTON C, et al. Collective unconscious: how gut microbes shape human behavior[J]. J Psychiatr Res, 2015, 63: 1-9. DOI: 10.1016/j.jpsychires.2015.02.021.
[44] WIKOFF W R, ANFORA A T, LIU J, et al. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites[J]. Proc Natl Acad Sci USA, 2009, 106(10): 3698-3703. DOI: 10.1073/pnas.0812874106.
[45] REIGSTAD C S, SALMONSON C E, RAINEY J F 3rd, et al. Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells[J]. FASEB J, 2015, 29(4): 1395-1403. DOI: 10.1096/fj.14-259598.
[46] YANO J M, YU K, DONALDSON G P, et al. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis[J]. Cell, 2015, 161(2): 264-276. DOI: 10.1016/j.cell.2015.02.047.
[47] SPECCHIO L M, IUDICE A, SPECCHIO N, et al. Citalopram as treatment of depression in patients with epilepsy[J]. Clin Neuropharmacol, 2004, 27(3): 133-136. DOI: 10.1097/00002826-200405000-00009.
[48] DEN BESTEN G, VAN EUNEN K, GROEN A K, et al. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism[J]. J Lipid Res, 2013, 54(9): 2325-2340. DOI: 10.1194/jlr.R036012.
[49] LU W, WU Z Z, ZHANG C, et al. Jujuboside A exhibits an antiepileptogenic effect in the rat model via protection against traumatic epilepsy-induced oxidative stress and inflammatory responses[J]. Evid Based Complement Alternat Med, 2022, 2022: 7792791. DOI: 10.1155/2022/7792791.
[50] CHENG Y H, MAI Q T, ZENG X, et al. Propionate relieves pentylenetetrazol-induced seizures, consequent mitochondrial disruption, neuron necrosis and neurological deficits in mice[J]. Biochem Pharmacol, 2019, 169: 113607. DOI: 10.1016/j.bcp.2019.08.009.
[51] LI D Y, BAI X Y, JIANG Y, et al. Butyrate alleviates PTZ-induced mitochondrial dysfunction, oxidative stress and neuron apoptosis in mice via Keap1/Nrf2/HO-1 pathway[J]. Brain Res Bull, 2021, 168: 25-35. DOI: 10.1016/j.brainresbull.2020.12.009.
[52] YEOM J S, PARK J S, KIM Y S, et al. Neonatal seizures and white matter injury: Role of rotavirus infection and probiotics[J]. Brain Dev, 2018, 40(6): 470-477. DOI: 10.1016/j.braindev.2018.07.001.
[53] EOR J Y, SON Y J, KIM J Y, et al. Neuroprotective effect of both synbiotics and ketogenic diet in a pentylenetetrazol-induced acute seizure murine model[J]. Epilepsy Res, 2021, 174: 106668. DOI: 10.1016/j.eplepsyres.2021.106668.
[54] BUFFINGTON S A, DOOLING S W, SGRITTA M, et al. Dissecting the

contribution of host genetics and the microbiome in complex behaviors[J]. Cell, 2021, 184(7): 1740-1756.e16. DOI: 10.1016/j.cell.2021.02.009.
[55] TAHMASEBI S, ORYAN S, MOHAJERANI H R, et al. Probiotics and *Nigella sativa* extract supplementation improved behavioral and electrophysiological effects of PTZ-induced chemical kindling in rats[J]. Epilepsy Behav, 2020, 104(Pt A): 106897. DOI: 10.1016/j.yebeh.2019.106897.
[56] WATANANGURA A, MELLER S, FARHAT N, et al. Behavioral comorbidities treatment by fecal microbiota transplantation in canine epilepsy: a pilot study of a novel therapeutic approach[J]. Front Vet Sci, 2024, 11: 1385469. DOI: 10.3389/fvets.2024.1385469.
[57] VAN NOOD E, VRIEZE A, NIEUWDORP M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*[J]. N Engl J Med, 2013, 368(5): 407-415. DOI: 10.1056/NEJMoa1205037.
[58] FISCHER M, SIPE B, CHENG Y W, et al. Fecal microbiota transplant in severe and severe-complicated *Clostridium difficile*: a promising treatment approach[J]. Gut Microbes, 2017, 8(3): 289-302. DOI: 10.1080/19490976.2016.1273998.
[59] HE Z, CUI B T, ZHANG T, et al. Fecal microbiota transplantation cured epilepsy in a case with Crohn' s disease: The first report[J]. World J Gastroenterol, 2017, 23(19): 3565-3568. DOI: 10.3748/wjg.v23.i19.3565.
[60] LI X Y, LI J, JI J, et al. Gut microbiota modification by diosgenin mediates antiepileptic effects in a mouse model of epilepsy[J]. J Neurochem, 2024, 168(12): 3982-4000. DOI: 10.1111/jnc.16033.
[61] MENGOLI M, CONTI G, FABBRINI M, et al. Microbiota-gut-brain axis and ketogenic diet: how close are we to tackling epilepsy?[J]. Microbiome Res Rep, 2023, 2(4): 32. DOI: 10.20517/mrr.2023.24.
[62] PLUTA R, JABŁOŃSKI M. The ketogenic diet for epilepsy therapy in children: quo vadis?[J]. Nutrition, 2011, 27(5): 615-616. DOI: 10.1016/j.nut.2010.12.015.
[63] FAN Y Y, WANG H, LIU X Y, et al. Crosstalk between the ketogenic diet and epilepsy: from the perspective of gut microbiota[J]. Mediators Inflamm, 2019, 2019: 8373060. DOI: 10.1155/2019/8373060.
[64] BARZEGAR M, AFGHAN M, TARMAHI V, et al. Ketogenic diet: overview, types, and possible anti-seizure mechanisms[J]. Nutr Neurosci, 2021, 24(4): 307-316. DOI: 10.1080/1028415X.2019.1627769.
[65] KWAN P, BRODIE M J. Early identification of refractory epilepsy[J]. N Engl J Med, 2000, 342(5): 314-319. DOI: 10.1056/NEJM200002033420503.
[66] FREEMAN J M, KOSSOFF E H, HARTMAN A L. The ketogenic diet: one decade later[J]. Pediatrics, 2007, 119(3): 535-543. DOI: 10.1542/peds.2006-2447.
[67] MELØ T M, NEHLIG A, SONNEWALD U. Neuronal-glial interactions in rats fed a ketogenic diet[J]. Neurochem Int, 2006, 48(6/7): 498-507. DOI: 10.1016/j.neuint.2005.12.037.
[68] QIAO Y N, LI L, HU S H, et al. Ketogenic diet-produced β-hydroxybutyric acid accumulates brain GABA and increases GABA/glutamate ratio to inhibit epilepsy[J]. Cell Discov, 2024, 10(1): 17. DOI: 10.1038/s41421-023-00636-x.

Author Contributions: LI Jing was responsible for literature collection and organization, overall conceptual design, and manuscript writing; LIU Ziqi was responsible for manuscript quality review. This article has no conflicts of interest.

(Received: 2025-01-20; Revised: 2025-02-14)
(Editor: MAO Yamin)

Note: Figure translations are in progress. See original paper for figures.