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EDITED BY
Yiming Meng,
China Medical University, China

REVIEWED BY
Rohan Gupta,
University of South Carolina, United States
Ana Pamela Gómez-García,
National Institute of Cancerology (INCAN), Mexico
Ameer Luqman,
Chongqing University, China

*CORRESPONDENCE
Sixi Zhang,
sixi@jlu.edu.cn

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The role of gut microbiota dysbiosis in drug-induced brain injury: mechanisms and therapeutic implications

Jinghui Zhai[1], Yue Zhang[2], Shuyue Ma[2], Yingli Zhang[2], Miao Jin[2], Huiyu Yan[3] and Sixi Zhang[1,2]*

[1]Department of Clinical Pharmacy, The First Hospital of Jilin University, Changchun, Jilin, China, [2]School of Pharmaceutical Science, Jilin University, Changchun, Jilin, China, [3]Division of Clinical Research, The First Hospital of Jilin University, Changchun, Jilin, China

Drug-induced brain injury (DIBI) results from toxicity, interactions or misuse and is increasingly linked to gut-microbiota dysbiosis operating via the gut–brain axis. Disturbed microbial balance drives three core mechanisms—oxidative stress, neuroinflammation and metabolic dysfunction—leading to blood–brain barrier leakage, neuronal loss and cognitive impairment; antibiotics, antineoplastics and psychoactive drugs further promote bacterial translocation and systemic inflammation. Microbial metabolites and neurotransmitters also mediate post-injury anxiety and depression. Restoring microbial equilibrium with probiotics, prebiotics or microbiota transplantation attenuates these pathways and offers a promising therapeutic strategy for DIBI.

KEYWORDS

drug-induced brain injury, gut microbiota, gut-brain axis, neuroinflammation, blood-brain barrier

1 Introduction

Drug-induced diseases (DID) are abnormal physiological processes that arise during disease prevention, diagnosis, and treatment due to drug use, drug interactions, and the effects of the drugs themselves (Garnier et al., 2024). These medications can cause structural, metabolic, and functional changes, manifesting as abnormal signs, symptoms, and behaviors. It can result from various factors, including the drug itself, the patient's physical condition, and improper administration by medical personnel. If not promptly identified, pharmacologically induced disorders can lead to permanent injury, including death or permanent disability (Drug-Induced Liver, 2019). It also can affect multiple organ systems, including the liver, kidneys, heart, lungs, and brain (Aggrawal, 2015). Further in-depth research is essential to enhance our understanding and treatment of these conditions.

The severity of drug-induced brain injury is influenced by factors such as the type of drug, dosage, duration of use, and individual patient differences (Baucom et al., 2024). Commonly misused drugs, including inappropriate use of antibiotics (e.g., cephalosporins, penicillins, aminoglycosides, and macrolides) (Ritter et al., 2024), long-term use of antiepileptic medications, excessive consumption of sedative-hypnotics, and the use of antineoplastic and antipsychotic drugs, can adversely affect the central nervous system and contribute to drug-induced brain injury (Michaelis et al., 2024). This damage can be persistent and irreversible, with the harm to the central nervous system potentially

worsening even after discontinuation of the drug. In severe cases, this can lead to brain failure, disability, or death (Jain, 2021).

Recent studies have indicated a correlation between gut microbiota and drug-induced brain injury (Loh et al., 2024). The gut microbiota, primarily residing in the large intestine, constitutes the predominant microbial community in the human body and plays a crucial role in maintaining health (N-Acetylcysteine Modulates, 2016). It is involved in digestion, absorption, immune regulation, and metabolic processes and may also influence brain function and health through the gut-brain axis (PMC, 2017). An imbalance in the gut microbiota can alter the metabolism and excretion of drugs, increasing toxicity to the central nervous system and the risk of drug-induced brain injury (Mostafavi Abdolmaleky and Zhou, 2024). Therefore, maintaining the balance and stability of the gut microbiota is vital for preventing drug-induced brain injury and preserving overall health.

This paper aims to explore the interplay between drug-induced brain injury and gut microbiota, which may help uncover the pathogenesis of drug-induced brain injury. This research also holds significant potential for advancing medical progress, enhancing drug safety, and optimizing therapeutic efficacy.

2 The impact of intestinal dysbiosis on brain injury

The gut microbiota interacts with the central nervous system through the gut-brain axis, a bidirectional communication network involving neural, endocrine, and immune pathways (Schaible et al., 2025). Intestinal dysbiosis, defined as abnormalities in the composition and function of the gut microbial community (da Silva et al., 2025), is characterized by a reduction in beneficial bacteria and an increase in harmful bacteria. This imbalance disrupts the gut's homeostasis, leading to impaired barrier function and increased intestinal permeability. The resulting systemic inflammation and metabolic dysfunction have been associated with conditions like inflammatory bowel diseases, obesity, diabetes, and autoimmune disorders (Psychiatry, 2014).

Recent studies have uncovered links between gut dysbiosis and brain injuries, suggesting that targeting intestinal microecology may offer novel therapeutic avenues for neurological disorders. The specific mechanism is shown in Figure 1.

2.1 Inflammatory pathways

Dysbiosis triggers systemic inflammation through several mechanisms. Beneficial gut bacteria produce anti-inflammatory metabolites such as short-chain fatty acids (Intestinal Microbes, 2014), which maintain intestinal barrier integrity and modulate immune responses. Although the activation of TLR-4 on the intestinal epithelium by lipopolysaccharides from gut commensals has been considered part of homeostatic processes for decades, pathogenic bacteria can activate toll-like receptors (TLRs) on intestinal epithelial cells and immune cells, initiating pro-inflammatory signaling cascades (Xia et al., 2021). This leads to increased production of pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β, which can cross the blood-brain barrier (BBB) and exacerbate neuroinflammation (TNF-α, 2004). Neuroinflammation is a key contributor to various brain injuries, including traumatic brain injury, stroke, and neurodegenerative diseases (Liu et al., 2023).

2.2 Neuroendocrine regulation

The gut microbiota interacts with the central nervous system through the gut-brain axis, a bidirectional communication network involving neural, endocrine, and immune pathways (Schaible et al., 2025). Gut bacteria can influence BBB permeability by modulating the expression of tight junction proteins such as claudin and occludin (Ma et al., 2022). They also produce and metabolize neurotransmitters like serotonin, dopamine, and gamma-aminobutyric acid (GABA), which affect cognitive function, mood, and behavior (Borrego-Ruiz and Borrego, 2025). Dysbiosis alters this neuroendocrine regulation, potentially leading to cognitive dysfunction, mood disorders, and delayed recovery from brain injury (Ashique et al., 2024). Studies have shown that probiotic intake may help maintain the integrity of the gut and BBB, thereby improving these neurodegenerative diseases (Neuroimmunology, 2003).

2.3 Behavioral and psychological effects

A balanced gut microbiota is essential for maintaining mental health (Appleton, 2018). Brain injury can disrupt the gut microbiota composition, leading to an overgrowth of harmful bacteria and a reduction in beneficial species. This microbial imbalance may contribute to psychological issues such as anxiety and depression, which are common complications of brain injury (Guha et al., 2023). These psychological factors can, in turn, affect patient compliance with rehabilitation programs and overall recovery outcomes (Zhang et al., 2025).

The interaction between gut microbiota dysbiosis and brain injury represents a complex and dynamic relationship that warrants further investigation. Future research should focus on elucidating the specific microbial species and metabolic pathways involved in these mechanisms. Additionally, clinical studies are needed to evaluate the efficacy of interventions targeting intestinal microecology, such as probiotics, prebiotics, fecal microbiota transplantation, and dietary modifications, in promoting brain injury recovery. Understanding these aspects may lead to the development of innovative therapeutic strategies for neurological injuries, offering new hope for patients suffering from these conditions.

3 Mechanisms underlying drug-induced brain injury and gut microbiota

3.1 Oxidative stress

Drug metabolism generates free radicals, including reactive oxygen species (ROS) such as superoxide anions and hydroxyl

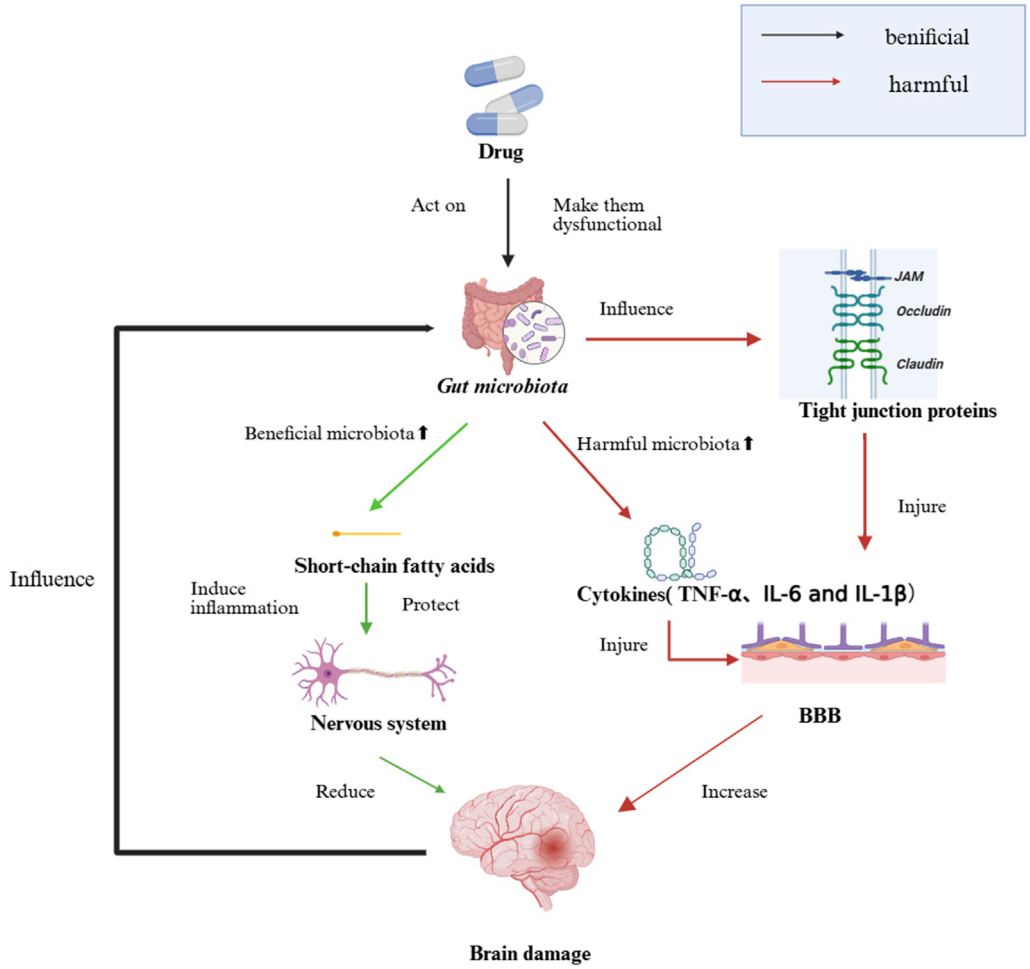

FIGURE 1
The Impact of Intestinal Dysbiosis on Brain Injury. Beneficial microbes strengthen tight-junction proteins and secrete short-chain fatty acids that protect the blood–brain barrier, whereas harmful microbes and their cytokines (TNF-α, IL-6, IL-1β) disrupt these junctions, fueling gut and brain inflammation and ultimately increasing neuronal injury.

radicals, which cause oxidative damage to cells. Cell membranes, rich in polyunsaturated fatty acids, undergo lipid peroxidation when exposed to free radicals. This disrupts membrane function and impairs transport mechanisms. Free radicals also damage DNA, causing strand breaks and base modifications, which can lead to cell death if not repaired (Jakubczyk et al., 2020).

In the nervous system, nerves are particularly vulnerable to oxidative stress due to their high metabolic activity and limited regenerative capacity (Michaelis et al., 2024). Accumulated free radicals can overwhelm neuronal antioxidant defenses, causing dysfunction and death (Chandimali et al., 2025). Chemotherapy drugs, for example, induce oxidative stress that directly harms nerve cells, contributing to neuropathies and cognitive impairments (Cauli, 2021).

Drugs can disrupt the gut microbiota balance, which alters microbial metabolite production, reducing beneficial short-chain fatty acids and increasing harmful substances (Garg and Mohajeri, 2024). The resulting impaired gut barrier function allows bacterial endotoxins into the bloodstream, activating immune cells and triggering inflammation, which further elevates ROS levels (Microbiome, 2009). This inflammatory response can become chronic, disrupting synaptic transmission and inducing neuronal apoptosis, ultimately contributing to brain injury (Dash et al., 2025).

3.2 Metabolic disorder

Drugs have the potential to interfere with normal metabolic processes in the body. This interference can lead to abnormalities in various metabolites, including sugars, fats, and proteins (Bio-Regulation, 2017). Experimental studies have demonstrated that drug-induced gut microbiota dysbiosis can significantly alter the host's metabolite profile, thereby affecting central nervous system (CNS) function. For instance, antibiotics (such as ciprofloxacin) and immunosuppressants (such as tacrolimus) increase the abundance of *Clostridium* spp. in the gut, leading to a 2.8-fold elevation in serum concentrations of the neurotoxic metabolite indoxyl sulfate (IS). IS can activate the microglial TLR4/ROS pathway, resulting in

hippocampal neuronal apoptosis and a 35% decrease in cognitive function scores in animal models (Kwart et al., 2019a). On the other hand, antipsychotic drugs (such as olanzapine) cause a 40% reduction in the phylum *Bacteroidetes*, leading to a 60% decrease in the levels of neuroprotective short-chain fatty acids (SCFAs), particularly butyrate. Supplementation with butyrate effectively restores mitochondrial complex I activity and improves energy metabolism in the prefrontal cortex (as indicated by a 22% increase in glucose uptake on PET-CT) (Lu et al., 2021).

However, there remains a significant gap in direct causal evidence for DIBI in humans: prospective cohort studies confirming the causal chain between microbiota metabolite changes and neural injury are currently lacking, with existing evidence primarily derived from animal models or correlational clinical studies (e.g., a positive correlation between serum IS levels and white matter lesion volume in stroke patients [r = 0.68]) (Wang et al., 2022). Based on this, we propose a rate-limiting hypothesis—when CNS energy supply is compromised (e.g., due to mitochondrial dysfunction) and neurotoxic metabolites continue to accumulate, this may synergistically trigger neurological dysfunction (Figure 2). This hypothesis has received indirect support from preclinical models of Alzheimer's disease (where butyrate deficiency increases Aβ deposition by 50% and IS infusion leads to a 30% decrease in synaptic density) (Kwart et al., 2019b), but further experimental validation is still needed in the context of DIBI.

Based on this rationale, it is further hypothesized that drug-induced metabolic disturbances, which can exacerbate the aforementioned shifts in metabolite profiles, may increase the risk of DIBI by enhancing neural vulnerability. This heightened vulnerability could render neurons more susceptible to the toxic effects of drugs or their metabolites, thereby contributing to the development or progression of brain injury. However, it is important to emphasize that this hypothesis requires further validation through rigorous experimental studies and clinical investigations to fully elucidate the underlying mechanisms and to develop effective therapeutic strategies (Microbiota in Neurological, 2015). Understanding the complex relationship between drug-induced metabolic disturbances and brain injury is essential for developing strategies to prevent and mitigate these adverse effects.

3.3 Disruption of the blood-brain barrier

The BBB serves as a critical protective interface that prevents the entry of exogenous substances and endogenous toxins into the brain parenchyma (Alaqel et al., 2025). However, certain medications, such as antiviral and antituberculosis drugs, have been shown to compromise BBB integrity by penetrating this protective barrier and impairing its function (Hahn et al., 2017).

The gut microbiota plays a regulatory role in maintaining BBB integrity (Ma et al., 2022). When drugs disrupt the gut microbiota, it can lead to intestinal epithelium imbalance. This disruption facilitates the release of toxic metabolites and pro-inflammatory cytokines, which subsequently activate endothelial cells and damage the BBB (IL-1β, 2016).

Additionally, some drugs can interfere with the metabolic process of tryptophan, an amino acid with important neurological functions (Luo et al., 2024). This interference increases BBB permeability, allowing the translocation of gut microbiota, inflammatory factors, and neuroactive metabolites into the brain. The resulting disruption of immune homeostasis creates a toxic inflammatory environment that can alter brain morphology and contribute to various neurological diseases (Targeting the blood-brain, 2016; dysbiosis).

3.4 Autonomic nervous system

The autonomic nervous system regulates visceral organs, smooth muscles, and cardiac muscles to maintain internal stability (Valenza et al., 2025). Changes in the gut microbiota can significantly impact this system. Drugs like antibiotics and nonsteroidal anti-inflammatory drugs alter gut microbiota composition, disrupting the gut-autonomic nervous system equilibrium.

Gut microbes influence neuronal function by modifying neurotransmitter synthesis and release, such as GABA (Qu et al., 2024). Dysbiosis can disrupt GABA synthesis, hindering neural transmission and normal neuronal activity (Alzheimer's disease, 2020). The gut microbiota may also regulate the autonomic nervous system through the gut-brain axis, affecting stress responses, emotions and potentially causing psychiatric disorders (Mallick et al., 2025).

Paul A. Muller et al. identified a group of vagal neurons projected to the distal gut that play an afferent role in the regulation of sympathetic activity by the gut microbiota, using chemogenomic manipulation, translational profiling, and anterograde tracing techniques. In addition, sensory nuclei in the brainstem were found to be activated in response to microbial absence, while efferent sympathetic glutamatergic neurons regulate gastrointestinal trafficking. These results suggest that the gut microbiota controls the activation of intestinal external sensory nerves through the gut-brain circuit dependently (Microbiota, 2024). The specific mechanism is shown in Figure 2.

4 Integrative summary: gut-brain axis contributions to brain injury

4.1 Impaired intestinal barrier function and systemic inflammation

The gut microbiome regulates neuroinflammation, neurotransmitter synthesis, mitochondrial function, and intestinal barrier integrity through the microbiome-gut-brain axis (Mahbub et al., 2024). Dysbiosis disrupts the intestinal barrier, increasing permeability ("leaky gut") and allowing bacterial products (e.g., LPS) to enter systemic circulation (Shukla et al., 2025). This triggers primary inflammatory cascades, including myeloid cell activation (e.g., macrophages) and TREM-dependent neuroinflammation, ultimately contributing to neuronal damage (Zhao et al., 2023; TREM, 2021), as shown in Figure 3.

Off-target effects further exacerbate this process. For instance, microbial metabolites (e.g., SCFAs, trimethylamine N-oxide [TMAO]) modulate systemic immunity via TLR signaling and vagal neurotransmission, indirectly influencing BBB permeability

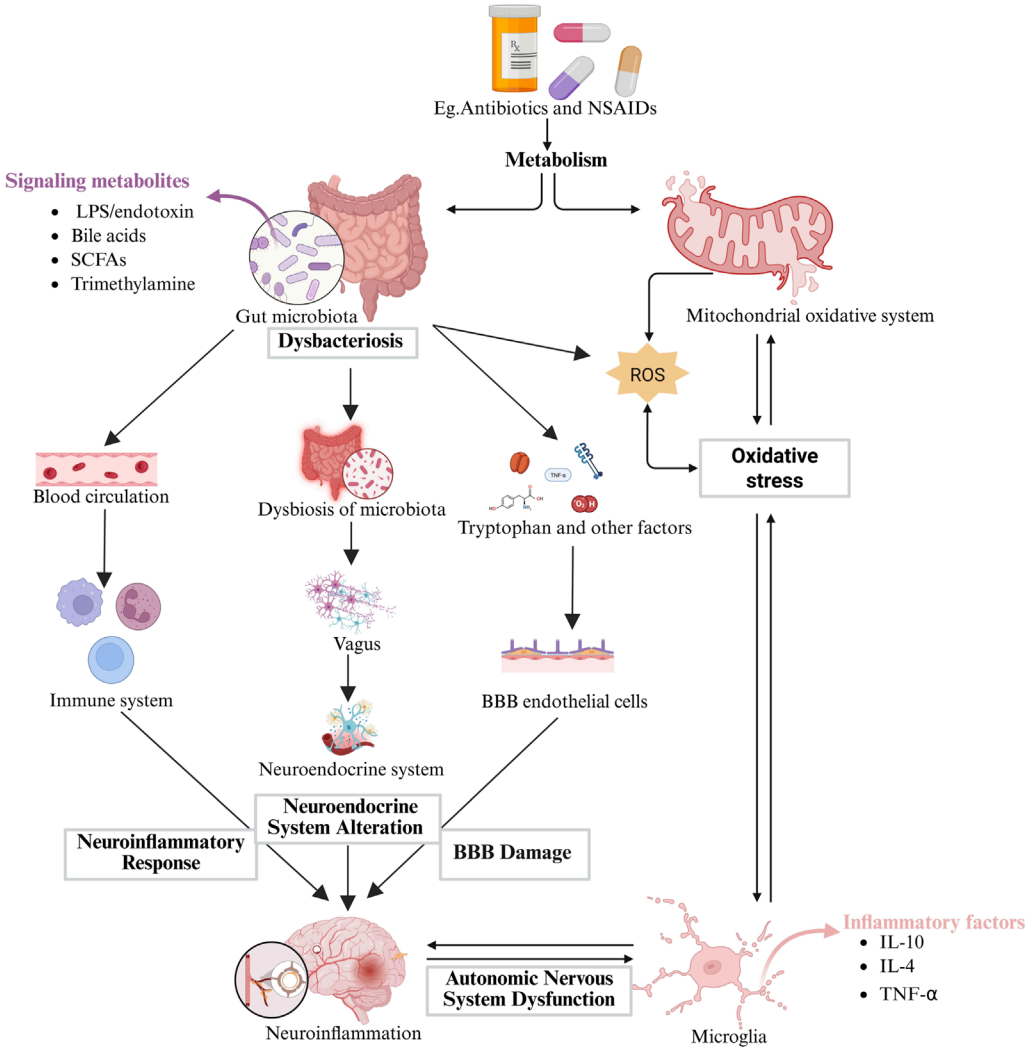

FIGURE 2
Mechanisms of Drug-Induced Brain Injury via Gut Dysbiosis. Oxidative Stress: ROS generated during drug metabolism can damage cellular membranes and DNA. This damage is exacerbated by an imbalanced gut microbiota. The imbalance reduces the production of beneficial metabolites such as SCFAs while increasing the release of harmful substances. This process impairs the integrity of the BBB and induces neuronal apoptosis. Metabolic Disturbances: Drugs can interfere with host metabolic processes, leading to the accumulation of neurotoxic substances and imbalances in energy metabolism. These changes may contribute to cognitive dysfunction and neurodegenerative disorders. Neuroinflammatory Responses: Gut dysbiosis facilitates the translocation of bacterial components such as LPS, and metabolites into the systemic circulation. This activates the immune system and leads to the release of pro-inflammatory cytokines, which further compromise the integrity of the BBB and exacerbate inflammation in the central nervous system. Additionally, the gut microbiota indirectly modulates brain function by regulating the autonomic nervous system and neuroendocrine pathways, such as influencing the synthesis of neurotransmitters like GABA and serotonin. This further aggravates cerebral damage.

and neuroinflammation (Eshleman et al., 2024; Luqman et al., 2024). Medications like antibiotics and NSAIDs disrupt microbial homeostasis (Cully, , 2019; Goyal et al., 2024), while dysbiosis-derived LPS activates peripheral immune responses, amplifying neuroinflammatory pathways (hypoxia, 2016). These secondary mechanisms link gut barrier dysfunction to neurodegenerative (e.g., Alzheimer's disease) and neuropsychiatric disorders (e.g., depression) (El-Hakim et al., 2022).

Additionally, gut-immune interactions facilitate prion-like protein translocation (Dysbiosis, 2019), highlighting the interplay between primary barrier disruption and off-target CNS effects.

4.2 Gut-derived RNA and epigenetic regulation

The gut microbiota regulates host physiology through primary RNA-mediated mechanisms, including non-coding RNAs (miRNAs, siRNAs) that modulate intestinal barrier function and inflammatory responses (Chen et al., 2021; Maazouzi et al., 2025; Liu et al., 2016). For example, fecal miRNAs from intestinal epithelial cells directly regulate bacterial gene expression, and their depletion exacerbates colitis (Liu et al., 2016).

Off-target systemic effects emerge when gut-derived RNAs or metabolites (e.g., four-ethylphenyl sulfate [4EPS]) enter circulation,

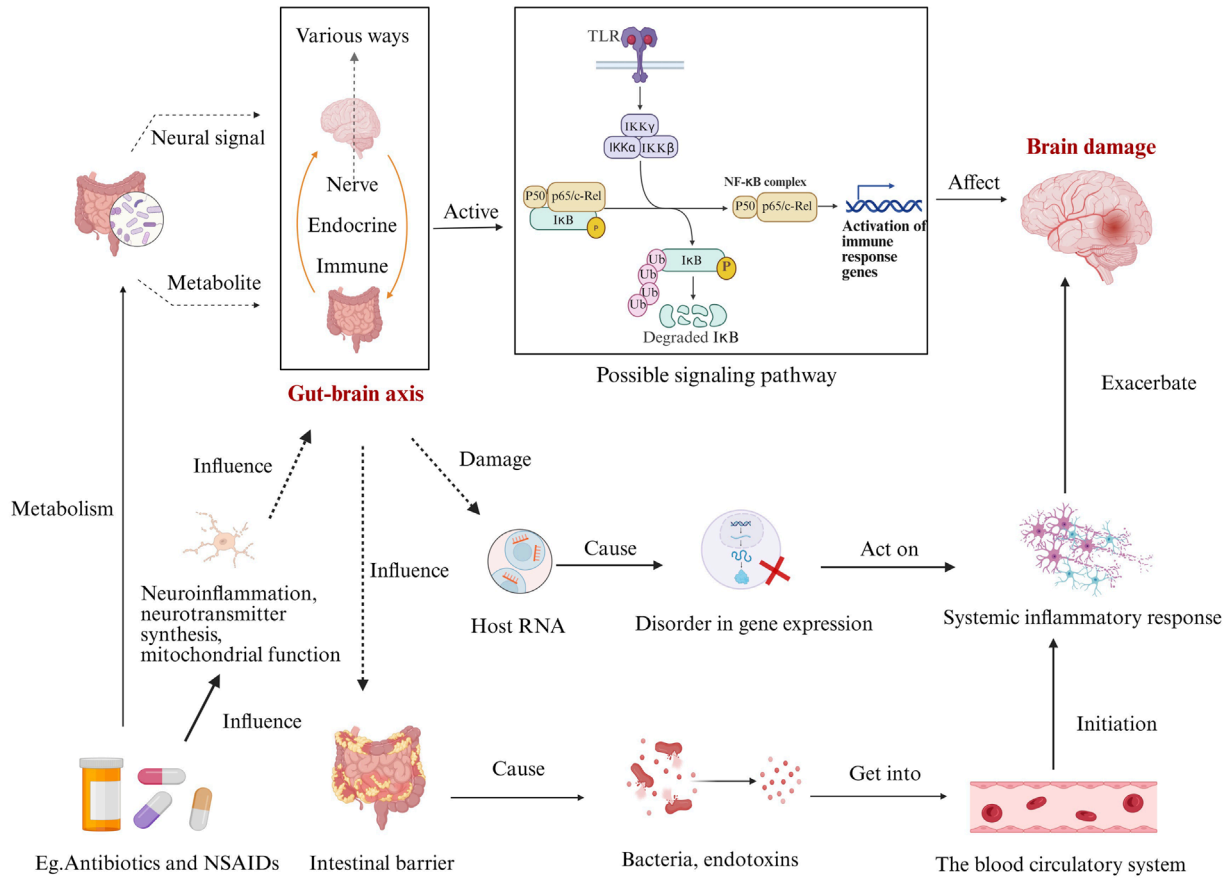

FIGURE 3
Disruption of the Gut-Brain Axis by Drugs. This diagram illustrates how drugs, impact neuroinflammation, neurotransmitter synthesis, and mitochondrial function, thereby influencing the gut-brain axis. These effects can lead to intestinal barrier damage, allowing bacteria, endotoxins, and other substances to enter the bloodstream. This triggers systemic inflammatory responses and disrupts host RNA gene expression, both of which affect the brain via the gut-brain axis. Meanwhile, activation of the gut-brain axis through signaling pathways like TLRs can activate immune response genes, potentially causing brain injury. In turn, brain injury can exacerbate systemic inflammatory responses, creating a complex interplay between the gut and brain.

cross the BBB, and alter microglial activity or synaptic plasticity (Metabolite alters brain, 2017). Microbial small RNAs may also indirectly influence neurorepair processes by modulating peripheral immunity (Bi et al., 2020) or epigenetic pathways (e.g., SCFA-mediated histone deacetylation) (Eshleman et al., 2024).

Diet and stress further shape these interactions, as microbiota composition dictates metabolite profiles (e.g., SCFAs, TMAO) with divergent effects on neuroinflammation (He et al., 2020; Hasan and Yang, 2019). While primary RNA regulation occurs locally in the gut, off-target CNS effects underscore the therapeutic potential of targeting gut-derived molecules (e.g., probiotics, miRNA mimics) (Cunningham et al., 2021).

5 Limitations of animal models

Although animal studies have provided important insights into the interaction between drug-induced brain injury and gut microbiota dysbiosis, caution is needed when applying these findings directly to humans. There are significant differences between animal models and humans in terms of physiology, genetics, metabolism, and immune response, which can impact the clinical relevance of research findings. The genetic background of animal models is relatively simple, while humans have a high degree of genetic diversity, which may affect individuals' responses to drugs and changes in gut microbiota. In addition, animals under laboratory conditions typically live in controlled environments, while humans are exposed to complex and variable environments, including diet, lifestyle, exposure to microorganisms, and other environmental factors that may affect gut microbiota and drug response. Therefore, although animal studies provide a foundation for understanding drug-induced brain injury and gut microbiota dysbiosis, future research needs to further explore the applicability of these findings in humans, validating and optimizing gut microbiota-based treatment strategies through clinical trials and population studies.

6 Conclusion

Our review underscores the complex interplay between DIBI and gut microbiota dysbiosis, highlighting the gut-brain axis as

a critical mediator. Key mechanisms include BBB dysfunction, oxidative stress, neuroinflammation, and metabolic disturbances driven by gut microbiota imbalance.

However, current research is limited by a predominance of preclinical studies and a lack of large-scale clinical trials. Future work should focus on elucidating the molecular underpinnings of this relationship and conducting robust clinical trials to validate microbiota-targeted therapies. Addressing these limitations and exploring personalized treatment strategies will advance neurogastroenterology and improve patient outcomes.

Author contributions

JZ: Conceptualization, Investigation, Writing – original draft, Writing – review and editing, Funding acquisition. YuZ: Data curation, Visualization, Writing – original draft. SM: Data curation, Writing – original draft. YiZ: Data curation, Writing – original draft. MJ: Data curation, Writing – original draft. HY: Funding acquisition, Visualization, Writing – review and editing. SZ: Conceptualization, Funding acquisition, Investigation, Writing – review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

BBB	blood-brain barrier
ROS	reactive oxygen species
LPS	lipopolysaccharide
IL	interleukin
IFN	interferon
GABA	γ-aminobutyric acid
NSAIDs	non-steroidal anti-inflammatory drugs
IBS	Inflammatory bowel syndrome
miRNA	microRNA
siRNA	small interfering RNA
DID	drug-induced diseases
SCFAs	short-chain fatty acids
TNFα	tumor necrosis factor alpha
TREM	triggering receptor expressed on myeloid cells
GPR	G-protein-coupled receptor
IBS	Inflammatory bowel syndrome
RNA	ribonucleic acid
CNS	central nervous system
IMM	immune-mediated mechanism
TBI	Traumatic brain injury
FMT	Fecal microbiota transplantation
NAD	Nicotinamide adenine dinucleotide
DCs	dendritic cells
CTLs	Cytotoxic T lymphocytes
APCs	antigen-presenting cells
ICI	Immune checkpoint inhibitors
ODN	oligonucleotides
GF	germ-free
ER	endoplasmic reticulum
COAD	colorectal
CRC	colorectal cancer
CTX	cyclophosphamide
Rag2	Recombination Activating Gene 2