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REVIEW

# From Microbial Homeostasis to Systemic Pathogenesis: A Narrative Review on Gut Flora's Role in Neuropsychiatric, Metabolic, and Cancer Disorders

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**Abstract:** As a pivotal ecological regulator in humans, the gut microbiota profoundly participates in the pathological processes of neurodegenerative diseases, psychiatric disorders, metabolic syndromes, and cancers through metabolite exchange, epigenetic regulation, and gut-brain axis signaling. This review focuses on analyzing relationships between gut microbial communities and four major disease spectra: neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, Huntington's disease)—revealing microbiota-derived lipopolysaccharide activation of microglia and gut-brain transmission pathways of α-synuclein; mental health disorders (depression, schizophrenia, bipolar disorder)—elucidating dysregulated tryptophan metabolism and gut-derived neurotransmitter imbalances; metabolic diseases (obesity, diabetes, gout)—analyzing molecular mechanisms by which short-chain fatty acids regulate insulin sensitivity and uric acid metabolism; malignant tumors (lung cancer, breast cancer, prostate cancer)—exploring microbial remodeling of immune checkpoint inhibitor responses and regulatory effects on estrogen metabolism. We integrate existing evidence to systematically expound the roles of gut microbiota alterations in the pathogenesis of neurodegenerative diseases, psychiatric disorders, metabolic dysregulation, and malignant tumors, with in-depth analysis of mechanisms through which dysbiosis promotes disease progression, aiming to provide a theoretical foundation and scientific recommendations for developing microbiota-targeted precision intervention strategies (including, but not limited to synthetic microbial community transplantation and metabolite-directed regulation).

**Keywords:** microbiota, immune regulation, neuromodulation, metabolic balance, imbalance of intestinal flora homeostasis

## Introduction

The human body constitutes a complex symbiotic ecosystem. Microbial communities colonizing distinct anatomical sites form dynamic cross-kingdom networks that are essential for maintaining physiological homeostasis. Among these, the gut microbiota (GM) represents the functionally most sophisticated microbial consortium, whose metabolic potential exceeds the human genome by two orders of magnitude. Through continuous bidirectional molecular crosstalk—encompassing metabolite exchange, epigenetic regulation, and genetic material transfer (eg, horizontal gene transfer)—the GM orchestrates fundamental biological processes ranging from nutrient metabolism and immune maturation to neuroendocrine modulation, effectively serving as a multifunctional virtual endocrine organ.[1–3]

Accumulating evidence underscores the dual role of the gut microbiota as both a guardian of mucosal health and an instigator of systemic diseases.[4,5] Its metabolic arsenal—encompassing xenobiotic detoxification, secondary bile acid

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biotransformation, and synthesis of neuroactive tryptophan derivatives—establishes the gut microbiota as a core dynamic regulator of host homeostasis.[6–8] Nevertheless, the delicate equilibrium of host-microbiota symbiosis remains vulnerable to modern ecological perturbations. Epidemiological studies have consistently documented associations between gut dysbiosis and multifactorial pathological conditions, including metabolic disorders characterized by insulin resistance, neurological diseases involving gut-brain axis dysregulation, and autoimmune disorders accompanied by mucosal immune abnormalities.[9,10] Paradoxically, while clinical investigations continue to identify disease-associated microbiome signatures across populations, the elucidation of causal mechanisms remains hindered by interindividual genomic variations, lifestyle-dependent microbial adaptations, and multidimensional confounding factors influencing host-microbe crosstalk.[11]

This review systematically synthesizes cutting-edge research findings to comprehensively elucidate the multidimensional mechanistic roles of gut microbiota across four major disease spectra: neurological disorders (Alzheimer's disease, Parkinson's disease, Huntington's disease), mental health disorders (depression, schizophrenia, bipolar disorder), metabolic diseases (obesity, diabetes mellitus, postmenopausal osteoporosis, gout) and tumorigenesis processes (lung cancer, breast cancer, prostate cancer). Through cross-spectrum comparative analysis, we strive to uncover evolutionarily conserved microbe-host interaction paradigms, thereby constructing a translational medicine framework bridging mechanistic interpretation and therapeutic innovation.

## Gut Microbiota and Neurological Disorders

The bidirectional interplay between the gastrointestinal (GI) tract and the central nervous system (CNS) has long been a cornerstone of medical research. This relationship, termed the gut-brain axis, exemplifies the profound interdependence of these systems.[12] Growing evidence suggests that the composition of the GM undergoes marked changes in various neurological disorders, with these changes closely associated with the relative abundance of specific microorganisms.[13] However, the GM is not only closely associated with gastrointestinal disorders but also linked to a range of neurological disorders.[14] Factors such as stress, mode of delivery, probiotic effects, biological clock regulation, dietary habits, and occupational and environmental exposures have been implicated in the bidirectional interactions between the GM and brain function, commonly referred to as the "microbiota-gut-brain axis." The microbiota plays a crucial role in the bidirectional communication within this axis, influencing both gut and brain function.[15,16] Research employing rodent models has demonstrated that gut microbiota significantly influences neuroinflammation, neurodevelopment, emotional regulation, and behavioral outcomes.[17–19] The GI tract and CNS are continuously exposed to a diverse array of signaling stimuli, both environmental and intrinsic to the body. These stimuli play a crucial role in maintaining the intricate balance necessary for optimal functioning of both systems.[20,21] While C-fiber mediated viscerosensory transmission via vagal and sympathetic afferents was traditionally considered the principal pathway for gut-brain communication,[22,23] contemporary research has identified gut microbiota-derived metabolites as essential signaling mediators in this axis.[24] Notably, microbial dysbiosis characterized by reduced butyrate-producing taxa has been mechanistically linked to inflammatory bowel diseases (IBD), primarily through disruption of gut-vascular barrier integrity and subsequent bacterial translocation.[25,26]

### Intestinal Microbiota Imbalance and Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder and the predominant cause of dementia among older adults.[27] Activation of microglia and imbalance in neuronal calcium homeostasis, triggered by amyloid β-protein (Aβ) deposition, are considered key mechanisms in AD development.[28] The GM performs vital physiological functions in the human body by activating pattern recognition receptors (PRRs) on innate and adaptive immune cells through constant interaction with the host immune system.[29] Notably, intracerebral LPS administration in mouse models has been associated with elevated amyloid-beta (Aβ) levels in the hippocampus, correlating with cognitive deficits.[30] These findings provide significant evidence for LPS's role in promoting amyloid fibril formation, indicating that intestinal inflammation may play a pivotal role in the pathogenesis of AD (Figure 1).[31] Dubosiella enrichment has been shown to mitigate AD progression through palmitoleic acid biosynthesis, with this anti-inflammatory lipid mediator demonstrating neuroprotective efficacy against neural metabolic dysregulation.[32] Recent studies have revealed a close link between the worsening of systemic inflammation, neuroinflammatory processes, and the increase in proinflammatory GM. Considering that an imbalance

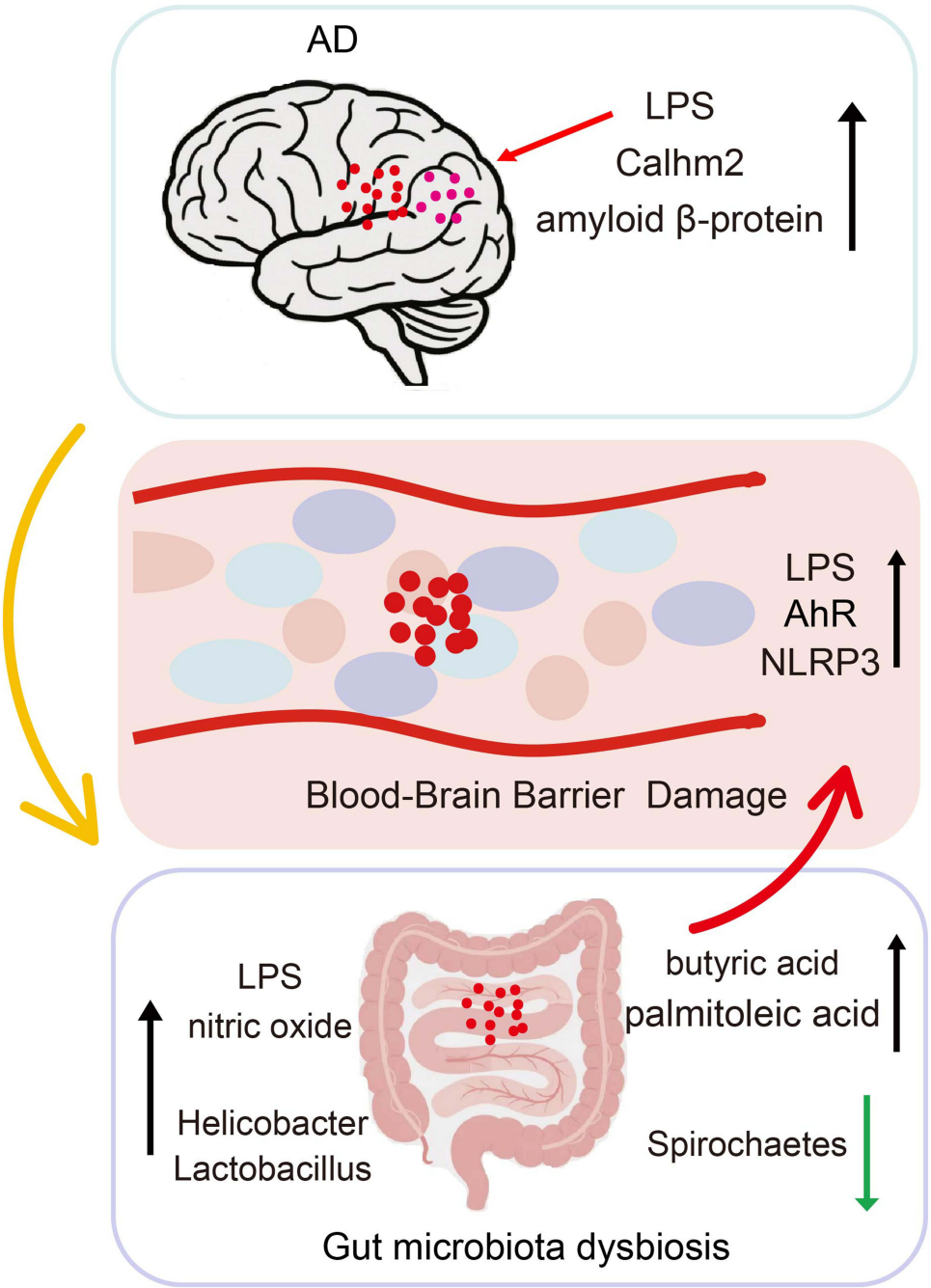


**Figure 1** LPS exposure significantly elevates hippocampal β-amyloid (Aβ) levels, experimentally confirming that neuroinflammation directly drives core AD pathology. Gut microbiota dysbiosis manifests as increased abundance of Helicobacter spp. and decreased abundance of Spirochaetes phylum. This imbalance aggravates AD pathogenesis through triple pathways: Specific microbiota generate nitric oxide activating microglia → promoting neuroinflammation and aberrant Aβ/Tau deposition; Upregulated intestinal NLRP3 inflammasome expression → triggering systemic inflammatory cascades; Dysregulated aryl hydrocarbon receptor (AhR) signaling activation→ compromising blood-brain barrier integrity. Prebiotic intervention increases Lactobacillus spp. abundance, enhancing biosynthesis of palmitoleic acid and butyric acid, which delay AD progression through anti-inflammatory properties and neurometabolic regulation.

in GM can trigger a decrease in microglial activity, the microbiota's pathological activation may contribute to the progression of AD. Notably, specific gut microbiota generate nitric oxide (NO) and activate microglia, contributing to the progression of AD pathology (Figure 1).[33–35] Acute and chronic viral infections activate microglia, leading to cytokine release and neuroinflammation. This neuroinflammation can influence the pathological processes of amyloid-beta (Aβ) and tau proteins.[36–38]


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### Calhm2-Mediated Gut-Brain Axis Dysregulation in AD Pathogenesis

In a 5xFAD mouse model harboring five familial AD mutations, elevated expression of calcium homeostasis regulator protein 2 (Calhm2) was significantly reduced by either conventional or conditional microglial cell-specific knockdown, leading to a marked reduction in amyloid plaque deposition, neuroinflammation, and cognitive deficits, thereby identifying Calhm2 as a potential therapeutic target for AD (Figure 1).[39] The study identified that systemic changes resulting from gut microbiota dysbiosis, caused by reduced endogenous melatonin (EMR), may contribute to the development of AD and obesity.[40,41] Research has shown that periodontitis contributes to the development of AD through mechanisms involving the ingestion of salivary microbiota and communication between the GM and the brain in transgenic mouse models.[42] Microbe-derived metabolites from the GM have been found in the cerebrospinal fluid of AD patients. These metabolites correlate with AD biomarkers, such as phosphorylated tau and the tau/Aβ42 ratio, suggesting that the gut microbiota contributes to the pathogenesis of AD.[43–46]

Substantial differences in the GM composition were detected using 16S rRNA sequencing of fecal samples between APP transgenic mice and wild-type models.[47] The transgenic AD mouse model exhibited distinct GM profiles. Studies on germ-free mice demonstrated that amyloid plaques and neuroinflammation were absent in the absence of microbes. A strong correlation between GM dysregulation and AD-associated neuroinflammation was identified, with elevated expression of aberrant intestinal NLRP3 being positively correlated with the activation of peripheral inflammatory vesicles.[48] As AD progressed, peripheral inflammatory vesicles progressively exacerbated neuroinflammation. Significant changes in the GM composition were observed in young and old 5xFAD mice, characterized by an increased abundance of *Helicobacter* and a decreased abundance of thick-walled bacterial phyla. It was revealed that the prebiotic mannan oligosaccharide (MOS) increased the abundance of *Lactobacillus* and decreased the abundance of *Spirochaetes* (Figure 1). Furthermore, MOS increased the production of butyric acid and the levels of associated microorganisms (Table 1). Ecological imbalance of the GM exacerbates AD pathology by activating the aromatic hydrocarbon receptor (AhR) signaling, damaging blood-brain barrier (BBB) integrity.[48–50]

## The Gut Microbiome and Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder marked by the abnormal deposition of α-synuclein (α-syn) within nigrostriatal dopaminergic neurons, resulting in subsequent motor deficits and gastrointestinal dysfunction. The abnormal deposition of α-synuclein results in the accumulation of eosinophilic cytoplasmic inclusions, termed Lewy bodies.[30,51,56] The hallmark clinical manifestation of PD is motor dysfunction, characterized by muscle rigidity, resting tremor, bradykinesia, and postural instability.[57–59] The neurodegenerative pathogenesis of PD is primarily driven by the progressive accumulation of misfolded α-synuclein within the CNS. Progressive dopaminergic neuronal degeneration underlies the strong interplay between motor and non-motor symptoms in PD.[60] Non-motor symptoms encompass neuropsychiatric manifestations (eg, depression, dementia) and gastrointestinal disturbances, including constipation, sialorrhea, bowel dysfunction, nausea, and dysphagia.

**Table 1** Gut Microbiota and Neurological Disorders

| Name | Pathologic Features/Etiology | Altered Intestinal Flora | Related Influencing Factors | References |
|---|---|---|---|---|
| AD | Microglial activation and neuronal calcium ion homeostasis imbalance. | The relative abundance of Helicobacter increased. | The prebiotic mannose oligosaccharide increased the relative abundance of lactobacilli. | [45–47] |
| PD | Death of nigrostriatal dopaminergic neurons. | The abundance of Ackermania increased. | Inhibition of TLR4/MyD88/NF-κB signaling pathway by fecal microbiota transplantation administration. | [51–54] |
| HD | CAG trinucleotide repeat amplification in exon 1 of the huntingtin protein (HTT) gene on chromosome 4. | Elevated levels of Bacteroides. | Substances such as vanillin, and picrocrocin are expected to be considered potential biomarkers for HD disease. | [55] |

**Abbreviations**: AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease.

### Gut Microbiota-Mediated α-Synuclein Pathology in PD Pathogenesis

PD is increasingly recognized as a multisystemic disorder arising from the interplay of genetic susceptibility, environmental factors, and age-related decline. Research indicates that gastrointestinal dysfunction in PD patients is strongly associated with gut microbiota dysbiosis and pathological α-synuclein aggregation within the enteric nervous system.[61–63] Emerging evidence suggests that PD pathogenesis originates in the gastrointestinal tract, mediated by bidirectional host-microbiome interactions. While the gut-brain axis hypothesis provides a compelling framework, it's important to note that the temporal relationship between gut dysbiosis and PD onset remains debated. Some longitudinal studies have failed to demonstrate consistent microbial changes preceding clinical diagnosis. Notable microbial shifts include elevated abundances of *Akkermansia* spp., *Bifidobacterium* spp., and *Lactobacillus* spp., alongside decreased colonization by *Bacteroides* spp. And *Enterococcus faecalis*. The reported microbial alterations show considerable variability across populations, with recent systematic reviews highlighting geographical and methodological factors as major contributors to observed discrepancies.Furthermore, fecal microbiota transplantation suppressed the TLR4/MyD88/NF-κB signaling pathway in both the substantia nigra and colon of rotenone-induced PD mouse models[51–54] (Table 1). Translational caution is warranted as rodent PD models, while valuable for mechanistic studies, often utilize acute toxin exposures that differ fundamentally from human disease progression patterns.Up to 80% of PD patients exhibit gastrointestinal dysfunction, notably constipation, often preceding motor symptom onset by several years.[64–66] Idiopathic constipation represents a significant comorbidity in PD and is associated with neurodegenerative alterations in the enteric nervous system.[52–54] The presence of pathological α-synuclein aggregates in the enteric nervous system is hypothesized to represent an early biomarker of PD, preceding motor symptom manifestation.[57,58,60] The specificity of enteric α-syn as a PD biomarker requires further validation, given its reported presence in other neurodegenerative conditions and aging populations.This pathological process is associated with chronic constipation and structural/functional alterations in the gastrointestinal tract wall. The GM has been implicated in disrupting enteric neuronal homeostasis, potentially driving pathological α-synuclein aggregation.[67,68] These alterations are detectable during prodromal PD stages and proposed as potential biomarkers antecedent to motor symptom manifestation.[57,58,60] Numerous studies have explored the gut microbiota-PD relationship, focusing on microbial composition and disease progression. For instance, a 2020 cohort study identified a marked reduction in *Prevotella* spp. abundance and diminished representation of non-*Enterobacteriaceae* taxa in PD patient fecal samples.[52–54] Current human studies face methodological challenges, particularly regarding standardization of microbiota analysis protocols and adequate control for confounding variables like medication use and dietary habits.

## Composition of the Gut Microbiome and Huntington's Disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by motor, cognitive, and psychiatric symptoms, with disease progression modulated by diverse environmental factors. The HTT gene, encoding the huntingtin protein, is mapped to chromosome 4. Pathogenic expansion of the CAG trinucleotide repeat in exon 1 of the HTT gene drives HD pathogenesis, historically termed Huntington's chorea. The huntingtin protein is ubiquitously expressed, including in the central nervous system and peripheral tissues such as skeletal muscle and the intestinal tract. Notably, mutant huntingtin (mHTT) expression in the gastrointestinal tract induces dysmotility, chronic diarrhea, and malabsorptive pathophysiology.[69,70] In-depth investigations have revealed that mutant HTT may disrupt GM homeostasis, inducing dysbiosis—a microbial imbalance—which could exacerbate HD progression. Dysbiosis has been clinically documented in HD patients and experimentally linked to mutant HTT aggregation, behavioral abnormalities, and reduced lifespan in animal models. In summary, these findings collectively suggest that mutant HTT may act through GM disruption as a central pathogenic mechanism in HD development.[55]

In HD, *Aeromonas enterocolitica* and *Pilocarpus* have been associated with interleukin-4 (IL-4) and interleukin-6 (IL-6) concentrations, respectively.[69] In HD patients, α-diversity and β-diversity were increased compared with healthy controls. It should be noted that the reported increases in microbial diversity metrics show interstudy variability, with some cohort studies reporting contradictory trends depending on disease stage and medication regimens. In HD patients, cells that interact directly or indirectly with the GM are activated. Although further studies are needed, the hyperactivation of natural immune cells in the gut of HD patients may play a key role in gut dysbiosis. This suggests that intestinal dysbiosis in HD patients may be closely related to the overactivation of immune cells in the gut.[70] While compelling, the

causal relationship between immune cell activation and dysbiosis requires further elucidation, as current evidence cannot exclude the possibility of reverse causality or shared environmental triggers.Through integrated metagenomic and metabolomic analyses, Qian et al demonstrated that, at the genus level, *Bacillus*-like bacteria, *Fusobacterium, Paracoccidioides, Zeligia, Bifidobacterium*, and *Christensenella* exhibited increased abundance, whereas *Treponema* (Tear Spirochetes), *Roseburia, Clostridium, Ruminococcus,Brucella,Butyricicoccus,Agaricus,Phocaeicola,Coprococcus*, and *Fusicatenibacter* showed notably reduced abundance in individuals with HD. Subsequent metabolomic profiling identified dimethisterone, propylparaben, vanillin, tulipolide, *p*-hydroxymandelic acid, and heptasaponin as potential diagnostic or prognostic biomarkers for HD[55] (Table 1). The specificity of these metabolites as HD biomarkers warrants rigorous evaluation, given their known involvement in other neurodegenerative and inflammatory conditions.

## Gut Microbiota and Mental Health Disorders

The brain-gut axis is regulated through neuroendocrine systems (eg, HPA axis), immune signaling, and bidirectional neural pathways.[71] The HPA axis regulates immune responses through precise modulation of pro- and anti-inflammatory cytokine production. Conversely, neuromodulatory processes are predominantly mediated by the autonomic nervous system (ANS) — comprising parasympathetic (eg, vagal), sensory, and sympathetic fibers — and the enteric nervous system (ENS).[72] The ENS governs the functions of muscles, mucous membranes, and blood vessels within the GI tract, thereby regulating its overall activity.[73] Notably, more than 30 different neurotransmitters are involved in its function.[74,75] The ENS is histologically distinct from the peripheral nervous system (PNS), as its neuronal components lack ensheathment by connective tissue collagen or Schwann cells. Instead, these components are ensheathed by specialized glial cells phenotypically analogous to astrocytes in the CNS.[76]

The enteric nervous system primarily consists of the Meissner's plexus, located in the submucosa of the intestinal mucosa, and the Auerbach's plexus, located between the circular and longitudinal muscularis propria.[77] Due to its location, the ENS maintains close connections with the systemic immune defenses of both the gut-associated lymphoid tissues (GALT) and the mucosal-associated lymphoid tissues (MALT) through numerous neurotransmitters and cytokines. Neurotransmitters released by the enteric nervous system bind to receptors on Peyer's patches and lymphocytes. GALT, primarily composed of immune system lymphocytes, accounts for 70% of the total and plays a key role in the immune response to external antigens.[78–80] Meanwhile, microorganisms in the gut, including specific species of bacteria and fungi, synthesize and secrete various neurotransmitters that transmit signals to the GALT and ENS.[81] Hormonal regulation of brain-gut communication is primarily mediated by the HPA axis, also known as the stress axis, which regulates the stress response. The hypothalamus releases corticoliberin and antidiuretic hormone, which initiate a hormonal cascade along the HPA axis, prompting the anterior pituitary to release corticotropin (ACTH). ACTH travels through the bloodstream to the adrenal cortex, where it stimulates the secretion of glucocorticoids, including cortisol.[82–84] Existing research suggests a close association between intestinal flora and depression, schizophrenia, and bipolar disorder.

### Gut Microbiota and Depression

Depression is a common psychological disorder characterized by persistent feelings of sadness and apathy, typically lasting at least two weeks. The development of this disorder is influenced by a combination of genetic and environmental factors, including major life changes, family problems, and chronic health distress.[12,85] Depression is a leading cause of long-term disability and suicide worldwide. Major depressive disorder remains a leading cause of disability among psychiatric disorders worldwide. Increasing numbers of preclinical and clinical studies are focusing on the GM, including the composition of microorganisms and changes in their functions, such as metabolite production. These changes are referred to as dysbiosis and are strongly associated with the onset and development of depression, regulated through the gut-brain axis.[80]

The balance within Bacteroidetes was disrupted, evidenced by an increase in Bacteroidetes spp. abundance and a decrease in Brucella spp. and Streptococcus spp. colonies (Figure 2). A significant association exists between short-chain fatty acids and depression, with low levels observed in patients with major depressive disorder (MDD). However, supplementation with these fatty acids, particularly butyrate, can exert an antidepressant effect by enhancing intestinal permeability and improving the responsiveness of the HPA axis[80] (Table 2). It has also been demonstrated[90] that dietary

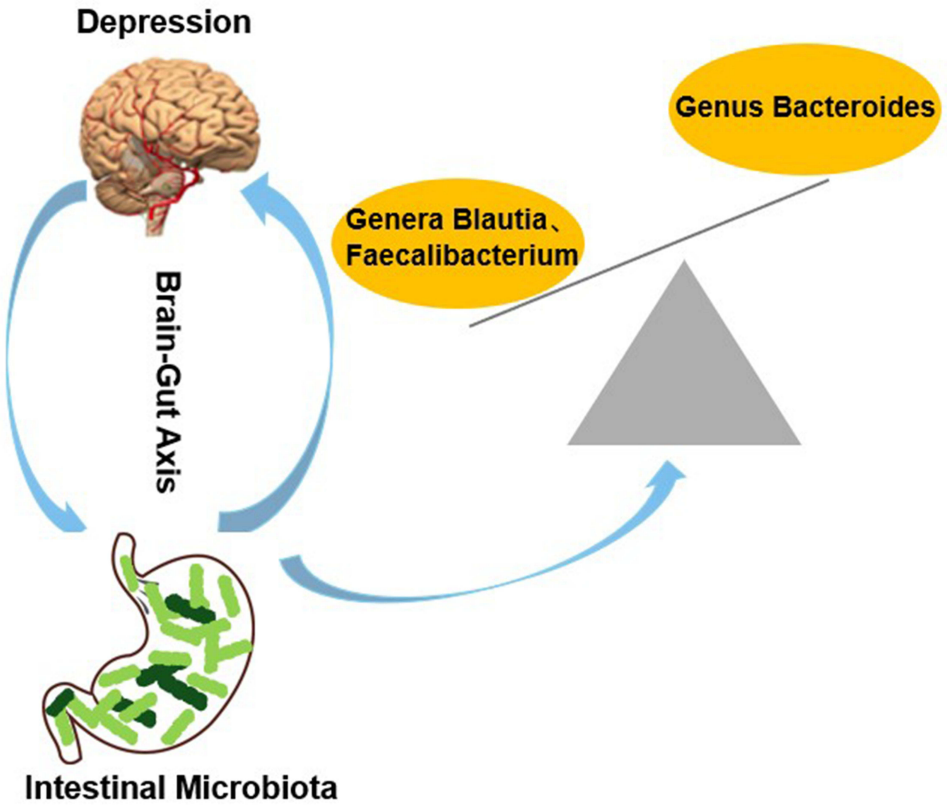


**Figure 2** Altered gut microbiota composition in depression and proposed bidirectional gut-brain axis mechanisms. In patients with depression, the relative abundance of Bacteroides increases, whereas the abundances of Brucella and Streptococcus decrease. Arrows depict key interactions: (Top-down, Brain→Gut) Cerebral inflammation under depression promotes gut microbiota dysbiosis via neuro-endocrine pathways; (Bottom-up, Gut→Brain) Gut dysbiosis exacerbates central nervous system inflammation; (Lateral, Synergy) Sustained gut-brain axis interactions drive the observed Bacteroides proliferation and reduction of Brucella and Streptococcus.

constituents, including probiotics (eg, Lactobacillus and Bifidobacterium), prebiotics (eg, dietary fiber and α-lactalbumin), synthetic prebiotics, postbiotics (eg, short-chain fatty acids), dairy products, and spices (eg, fruits, vegetables, and herbs), protect against mental disorders by enhancing beneficial gut microbiota and inhibiting harmful microbiota. In addition, Saccharomyces boulardii improves gut health, reduces depressive-like behaviors, decreases HPA axis hyperactivity, and alters the gut microbiota in hemiplegic spastic cerebral palsy (CP) rats.[91] Skonieczna-Zydecka et al[92] conducted an short-chain fatty acids(SCFAs) profiling study on 116 females aged 52.0 (±4.7) years and found that 40.52% of the participants had depression. The results showed that depressed patients had lower levels of propionic acid and higher levels of isocaproic acid compared to healthy controls. In the early stages of MDD, changes in the microbiota may occur, potentially triggering the onset of MDD. Over time, pathological changes in MDD can affect the intestinal environment, further exacerbating the ecological imbalance (Figure 2).

**Table 2** Gut Microbiota and Mental Health Disorders

| Name | Pathologic features/Etiology | Altered Intestinal flora | Related Influencing Factors | References |
|---|---|---|---|---|
| Depression | Genetic and environmental factors are both driven | Brucella spp. decreased | Supplementation with short-chain fatty acids may exert antidepressant effects | [80] |
| SCZ | Characterized by abnormalities in psychiatric function and behavioral disturbances | Proteus, Gram bacterium, and Lactobacillus were up-regulated | Decreased anti-inflammatory butyric acid-producing bacteria in patients with schizophrenia | [12,86–88] |
| BD | Mitochondrial dysfunction, oxidative stress, and abnormal calcium signaling | The presence of lactobacilli is directly related to higher levels of tryptophan | Regulation of neurotransmitter levels is affected | [89] |

**Abbreviations**: SCZ, Schizophrenia; BD, Bipolar disorder.


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### Multi-Target Microbiota Interventions for Depression via Gut-Brain Axis Modulation

Beyond probiotics, prebiotics, and dietary fibers that positively modulate depression pathogenesis, emerging research demonstrates that Clostridium butyricum reverses gut dysbiosis in inflammatory depression model mice, concurrently reducing proinflammatory cytokine levels and producing antidepressant-like behavioral improvements.[93] This finding aligns with clinical observations—adolescent depression patients exhibit significantly reduced abundance of short-chain fatty acid-producing bacteria (eg, Faecalibacterium, Blautia, Collinsella) in fecal samples, with restoration trends following sertraline intervention.[18] Mechanistic studies further reveal that proline supplementation exacerbates depression phenotypes by promoting microbial translocation, while human microbiota transplantation confirms this process involves prefrontal cortex GABA metabolic dysregulation and aberrant extracellular matrix gene expression.[94] Notably, Faecalibacterium prausnitzii not only serves as a potential diagnostic biomarker,[95] but its functional impairment (eg, via fecal microbiota transplantation from methylmercury-exposed mice) can induce depression-anxiety comorbidity,[96] highlighting the precision intervention value of microbiota modulation. Therapeutic strategy research transcends conventional paradigms: selective regulation of intestinal epithelial serotonin reuptake transporters specifically ameliorates mood-related behaviors;[97] the natural compound Icariside II (ICS II) enhances gut barrier integrity by enriching Akkermansia and Ligilactobacillus;[98] metformin reprograms serotonin metabolism via the microbiota-gut-brain axis;[99] and indole-3-propionic acid (IPA) inhibits ferroptosis through the NRF2/System xc-/GPX4 pathway, disrupting the depression-myocardial ischemia-reperfusion injury comorbidity[100]—jointly establishing a multi-target intervention network.

## Gut Microbiome and Schizophrenia

Emerging research explores the gut-brain axis bidirectional mechanisms.[101,102] Changes in microbial composition have been strongly linked to a broad spectrum of diseases, ranging from localized gastrointestinal disorders to respiratory, cardiovascular, and neurological disorders.[103–105] The microbiota has shown sensitivity to a wide range of intrinsic and extrinsic factors, including genetics,[106] modes of transmission,[107] dietary habits,[108] and infections and their treatment modalities[109] (Figure 3). Schizophrenia(SCZ) is a chronic and highly disruptive mental disorder characterized by abnormalities in mental functioning as well as behavioral deficits that show a high degree of individual variability.[86] A recent study, building on the traditional technique of gene-set enrichment analysis, employed data from a published study involving 33,426 SCZ patients and 32,541 healthy controls with genome-wide association study (GWAS) data. The study identified associations between specific microbial genera and SCZ, such as Desulfovibrio spp. and Mycobacterium spp., suggesting that these microbes may contribute to the pathogenesis of SCZ.[110] While this GWAS approach reveals important associations, the field is increasingly adopting longitudinal metagenomic sequencing to determine whether microbial changes precede symptom onset – a critical criterion for establishing causality. It should be emphasized that such observational data cannot exclude reverse causation, particularly given evidence that antipsychotic medications directly alter gut microbiota composition. Future studies combining microbial strain-level analysis with host immune profiling may better disentangle microbial drivers from disease consequences.

Studies examining the impact of the GM on SCZ spectrum disorders are generally limited by small sample sizes.[111] These studies have generally reported changes in microbial diversity in patients with SCZ compared to healthy controls, though findings remain inconsistent.[112] In a study involving 64 patients with SCZ and 53 healthy controls, 12 significantly different microbiota biomarkers were identified. In a study involving 64 patients with SCZ and 53 healthy controls, 12 significantly different microbiota biomarkers were identified.[113] However, this cross-sectional study had a small sample size and did not account for the effects of antipsychotic medication on the GM.

### Dynamic Microbial Dysbiosis in SCZ: Clinical Correlates and Therapeutic Implications

A study found elevated levels of *Lactobacillus* in individuals at high risk for SCZ.[106] Conversely, another study found decreased levels of *Lactobacillus* in patients with first-episode psychosis.[114] The study found that in the population of first-episode psychotic patients, microbial composition, particularly *Lactobacillaceae*, was strongly associated with disease severity. Follow-up after one year showed that patients with significant differences in microbial composition had lower remission rates compared to healthy controls, who exhibited higher remission rates.[87] Additionally, the study observed a decrease in *Bifidobacterium* and *E. coli* levels in patients. After 24 weeks of risperidone treatment, these

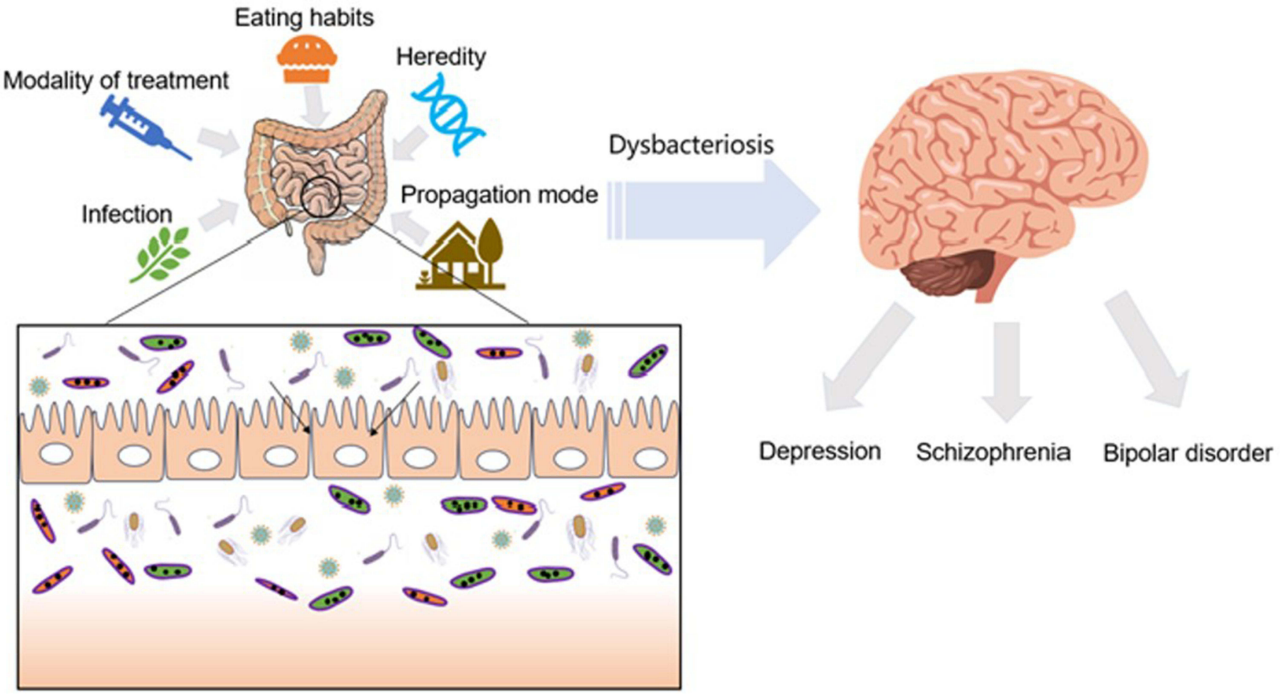


**Figure 3** Multifactorial disruption of gut microbiota homeostasis and its vicious cycle with CNS disorders via the gut-brain axis. Key factors (infections, therapeutics, diet, genetics, transmission patterns) collectively induce gut microbiota dysbiosis (arrows encircling intestine). This imbalance: Triggers intestinal barrier disruption: Pathobiont translocation (arrow downward) promotes systemic inflammation; Activates gut-brain signaling (arrow rightward): Dysregulated microbial metabolites modulate CNS function via neuroendocrine/immune pathways; Drives CNS dysfunction (arrow downward): Resultant neuroinflammation and neuronal abnormalities further perturb gut microbiota, reinforcing a pathological cycle that exacerbates depression, schizophrenia, and bipolar disorder.

levels increased, while *Lactobacillus* levels declined. A psychiatric pathology study involving patients with a disease duration of more than 10 years (age range: 12–56 years) found that decreased levels of *Ruminococcaceae* (Clostridiaceae) were associated with a reduction in negative symptoms. The study also observed that an increase in depressive symptoms was associated with a higher presence of *Mycobacterium anisopliae*.[88] Although a healthy microbiome typically exhibits a high degree of diversity,[115,116] in patients with SCZ, the oropharyngeal microbiome exhibited lower biodiversity compared to controls.[117] Additionally, studies on oropharyngeal phages (viruses) have shown elevated levels of phages and Lactobacillus acidophilus in patients with SCZ, which are positively correlated with an increased risk of co-morbid immune disorders compared to lower levels in non-psychiatric controls.[118]

## Gut Barrier Breakdown and Microbial Translocation in Schizophrenia Pathogenesis

RNA sequencing analysis revealed that gut-derived microbial products were more likely to enter the systemic circulation in patients with SCZ compared to non-psychotic controls. Moreover, the study observed an increased microbial diversity in the patients' blood. Furthermore, levels of genes associated with Chlamydia were significantly elevated in individuals with SCZ compared to healthy controls.[119] These findings may enhance our understanding of the pathophysiological mechanisms underlying SCZ. Additionally, other clinical studies have explored the permeability of blood biomarkers related to gastrointestinal tract infiltration.[111,120] The serological surrogate marker soluble cluster of differentiation (sCD) 14 was found to be significantly more prevalent in SCZ patients, with a 3.1-fold increase in the risk of bacterial translocation compared to healthy controls. Furthermore, sCD14 and lipopolysaccharide-binding proteins were significantly correlated with C-reactive protein levels in SCZ patients, suggesting shared inflammatory pathways. This implies that a compromised intestinal barrier may facilitate the entry of microbes and other markers into systemic circulation, thereby triggering a low-grade inflammatory state.[120] Zhuocan Li et al observed significant alterations in the microbial composition of patients with SCZ. Specifically, several microbial taxa exhibited a consistent upregulation, including Aspergillus, Gram-negative bacilli, Lactobacillaceae, Enterobacteriaceae, and Aspergillus spp. Concurrently, five taxa demonstrated consistent downregulation in patients, including Fusobacterium, E. faecalis, Bacillus roseus, and two

species of acidophilus. This microbial distribution pattern may reflect specific features of the microbial environment in SCZ patients. Moreover, GM alterations in SCZ patients are marked by a decrease in anti-inflammatory butyrate-producing genera and an increase in specific opportunistic bacterial genera and probiotics[86] (Table 2).

## Bipolar Disorder

Bipolar disorder (BD), also referred to as manic-depressive disorder, is a serious mental illness characterized by mitochondrial dysfunction, oxidative stress, and abnormal calcium signaling. It is primarily marked by the simultaneous occurrence of two extreme mood states: mania and depression. BD affects 45 million people worldwide. According to the National Institute of Mental Health, up to 50% of individuals with BD do not receive adequate mental health treatment, leading to over 2 million untreated cases in the United States. The progression of the disease, including relapse and worsening of bipolar symptoms, has become an increasing concern. These trends highlight the need for further research into potential preventive strategies for BD treatment.

Changes in the composition of the GM have been found to contribute to the development of neurological disorders, including bipolar affective disorder.[121–123] Studies have shown that stress, including social stress, can affect the composition of the GM. Moreover, bidirectional communication between the gut and the CNS plays a crucial role in the response to stress.[124–126] The body's stress response manifests in immune modulation, including cytokine release, and is closely associated with stress exposure and impaired gut barrier function. Experimental and clinical studies demonstrate that elevated stress levels correlate with increased intestinal permeability.[127,128] Furthermore, emerging evidence suggests that the blood-brain barrier (BBB)'s integrity is modulated by GM composition, where dysbiosis may induce BBB compromised integrity.[129] Research evidence indicates that specific gut bacterial taxa may contribute to weight dysregulation pathology in BD through modulation of lipid metabolism, energy homeostasis, and amino acid pathways.[130] Recent experimental studies further demonstrate that Roseburia intestinalis significantly increases production of the microbial metabolite homovanillic acid (HVA) by promoting Bifidobacterium longum colonization and proliferation. This metabolite suppresses synaptic autophagic hyperactivation by antagonizing aberrant degradation of LC3-II and SQSTM1/p62 proteins in hippocampal neurons, thereby preserving presynaptic membrane integrity and functional stability.[131] However, current evidence remains insufficient to establish causal-temporal relationships between gut microbiome alterations and BD, necessitating further elucidation of bidirectional mechanisms and potential confounders through longitudinal cohort studies or experimental models.

### Multi-Omics Reveals Tryptophan-Serotonin Axis Dysregulation in BD

Painold et al conducted a study that investigated the relationship between gut microbiota and BD[89] (Table 2). The gut-brain axis association underscores the potential role of specific GM as *psychobiotic agents* capable of influencing neurological function. Beyond cytokines, Lai et al (2023) explored the relationship between key neurotransmitter precursors—notably tryptophan—and BD. Utilizing shotgun metagenomic sequencing, the authors compared GM composition and genes linked to tryptophan (Trp) biosynthesis/metabolism across 25 BD patients and 28 healthy controls. Their findings demonstrated that BD patients displayed dysregulated tryptophan hydroxylase and aromatic aminotransferase activity, resulting in diminished Trp biosynthesis and, consequently, reduced serotonin production.[132] Shotgun metagenomics and longitudinal studies are propelling mechanistic research on the GM-bipolar disorder relationship into deeper dimensions. Shotgun methodology overcomes limitations of conventional 16S sequencing by precisely identifying aberrant functional genes. Longitudinal investigations dynamically track GM fluctuations to delineate causal relationships: multi-timepoint analyses capture temporal patterns linking microbial shifts with mood episodes and drug responses, while integrated metabolomics constructs "microbe-metabolite-symptom" dynamic networks, thereby revealing targeted intervention windows. These methodological innovations are driving a paradigm shift from correlational observations toward mechanistic exploration and clinical translation.

# Gut Microbiota and Metabolic Diseases

Metabolic disorders represent a mounting global health challenge, driven by their soaring prevalence. The GM orchestrates pivotal interactions with the host via the synthesis of diverse metabolites, originating from both exogenous

dietary substrates and endogenous host-derived compounds. Dysbiosis of the GM—alterations in its composition and functional capacity—is strongly implicated in the pathogenesis of metabolic disorders. Specific metabolites synthesized by gut microbiota—including bile acids, short-chain fatty acids, branched-chain amino acids, trimethylamine N-oxide, tryptophan, and indole derivatives—play critical roles in the pathogenesis of metabolic disorders. Over the past two decades, the global prevalence of metabolic disorders has surged, primarily attributed to excessive caloric intake and sedentary lifestyles. Metabolic disorders comprise a spectrum of interconnected pathologies, such as obesity, nonalcoholic steatohepatitis (NASH), dyslipidemia, impaired glucose tolerance, insulin resistance, hypertension. The co-occurrence of these conditions synergistically exacerbates cardiovascular disease -related morbidity and mortality.

## Obesity

Obesity, defined as excessive adiposity relative to height, is recognized by major international health organizations as a defining epidemic of the 21st century.[133] Obese individuals demonstrate reduced GM diversity relative to lean individuals, giving rise to a distinct profile of microbial metabolites that modulate systemic energy homeostasis and glucagon-like peptide-1 (GLP-1) secretion, thereby influencing metabolic dysfunction.[134] High-fat diets have been demonstrated to perturb GM composition and promote the development of GLP-1 resistance through disruption of enteric neuronal nitric oxide synthase (nNOS) activity, thereby compromising intestinal regulation of energy homeostasis and disrupting gut-brain axis signaling pathways.[135] The GM are central regulators of energy homeostasis, synthesizing SCFAs and liberating energy via dietary fiber fermentation. Furthermore, the GM augments intestinal nutrient absorption by stimulating intestinal villi angioneogenesis and suppressing adipokine-mediated lipoprotein lipase (LPL) activity during fasting, thereby facilitating triglyceride deposition in adipose tissue.[133]

*Lactobacillus spp*., key members of the small intestinal microbiota, have been demonstrated to modulate intestinal epithelial cells (IECs), thereby attenuating early-life diet-induced obesity. A *Lactobacillus*-derived metabolite, phenyl lactic acid (PLA), confers protection against metabolic dysfunction induced by early-life antibiotic exposure and high-fat diet (HFD) consumption via upregulation of peroxisome proliferator-activated receptor gamma (PPAR-γ) expression in small intestinal epithelial cells (SI IECs) (Table 3). [136]

## Diabetes

Emerging preclinical evidence has established a causal link between GM dysbiosis and the emergence of insulin resistance, a hallmark mechanism driving the pathogenesis of type 2 diabetes mellitus (T2DM).[144,145] This relationship encompasses multifactorial mechanisms, such as endotoxemia, compromised intestinal barrier integrity, dysregulated bile acid metabolism, and perturbed brown adipose tissue (BAT) distribution.[146] Elevated abundances of mucin-degrading *Akkermansia* spp. correlate with enhanced glucose homeostasis in individuals with early-stage T2DM.[147] These findings underscore the therapeutic potential of targeted modulation of GM composition to ameliorate metabolic dysfunction.

A synbiotic formulation containing *Bifidobacterium bifidum* and *Lactobacillus acidophilus* markedly lowered fasting blood glucose levels in T2DM patients, as evidenced by a randomized controlled trial.[148] Restoration of gut microbiota composition to a profile akin to healthy controls improved glycemic control, highlighting the therapeutic relevance of

**Table 3** Gut Microbiota and Metabolic Diseases

| Name | Connection with the Intestinal Flora | Associated Factors/Pathologies | References |
|---|---|---|---|
| Obesity | Lactobacillus spp. regulate intestinal epithelial cells (IEC) to limit obesity | Phenyllactic acid (PLA) protects the organism through the abundance of PPAR-γ | [136] |
| T2D | Decreased levels of Bifidobacteria, Akkermansia and Faecalibacterium | Reduction of Bradyrhizobium spp. is negatively correlated with glucose levels | [137–140] |
| PMO | The ratio of firmicutes/bacteroidetes increases significantly during estrogen deficiency | LGG therapy improves inflammation and mucosal damage | [141] |
| Gout | The relative abundance of Prevotella, Fusarium is increased | Dysbiosis of intestinal flora is associated with dysregulation of host urate degradation | [142,143] |

**Abbreviations**: T2D, Type 2 diabetes mellitus; PMO, Postmenopausal osteoporosis.

microbial modulation.[137] Patients with T2DM demonstrate markedly diminished GM alpha diversity and microbial abundance relative to healthy controls.[138,149,150] Individuals with prediabetes and T2DM exhibit distinct metabolic signatures and GM compositional profiles, reflecting progressive dysbiosis across clinical stages.[138,150] Compared to healthy controls, patients with T2D exhibit reduced levels of butyrate-producing bacteria, including *Bifidobacterium, Akkermansia*, and *E. faecalis*[139,149,151] as well as decreased levels of *Thick-walled bacteria, Clostridiaceae*, and *Streptococcus pepticus*. Additionally, a significant reduction in *Brucella* spp. was negatively correlated with HbA1c and glucose levels in patients with T2D[140] (Table 3).

During the onset of T2D, an increase in the phylum *Anabaena* and a decrease in the phylum *Thickettsia* have been identified.[138,150] In addition, there is a trend toward increased levels of Actinobacteria and Anabaena phyla,[139] as well as Lactobacillus[138,150] in patients with T2D. A diminished abundance of *Lactobacillaceae* has been observed in T2DM patients, and this reduction is associated with impaired glucagon-like peptide-1 (GLP-1) sensitivity.[152] Notably, elevated ratios of *Mycobacterium avium* to *Mycobacterium smegmatis* and *Prevotella* to *Bacteroides fragilis* were observed in T2DM patients, exhibiting a positive association with fasting blood glucose concentrations.[153]

In patients with type 1 diabetes (T1D), reduced proportions of *Bifidobacterium* and thick-walled bacilli phyla, as well as a downward trend in the *Bacteroides* phylum, have been observed. Conversely, elevated levels of *Dora* spp. (family *Trichoderma*) in patients with T2D are associated with chronic inflammation and may serve as indicators for high-risk T2D populations.[149] Collectively, these findings indicate that the microbiome plays a critical role in the pathogenesis of T2D. Bilen et al reported elevated abundances of *S. aureus* and *S. epidermidis* in the conjunctiva of T2D patients relative to controls, whereas animal models demonstrated that microbial dysbiosis correlated with heightened treatment resistance.[154] These findings underscore the significant role of the microbiome in T2D progression.[155]

## Postmenopausal Osteoporosis

Osteoporosis is a condition characterized by low bone mass and/or poor bone quality, which may progress to skeletal fractures that occur spontaneously or with minimal impact.[156] It is characterized by a reduction in trabecular bone volume and degradation of the microstructure of the medullary cavity.[157] Postmenopausal osteoporosis (PMO) is a condition resulting from estrogen deficiency, leading to a decrease in bone mass and deterioration of bone microstructure, which subsequently increases the risk of fragility fractures.[158] Menopause is a significant predisposing factor for osteoporosis in women, with the prevalence of the condition in women aged 50 and older projected to reach 13.6 million by 2030.[159] As the correlation between the gut and bone becomes increasingly evident, numerous therapeutic studies for postmenopausal osteoporosis are emerging, focusing on GM modulation as a potential therapeutic approach.The administration of *Lactobacillus rhamnosus* GG has been shown to alleviate osteoporosis in de-ovulated rats through modulation of the Th17/Treg balance and gut microbiota composition.[141] Furthermore, LGG treatment was found to ameliorate estrogen deficiency-induced inflammation and mucosal damage, while enhancing the expression of GLP-2 receptor (GLP-2R) and tight junction proteins (Table 3). 16S rRNA sequencing revealed a significant increase in the ratio of Thick-walled phylum to *Anthrobacterium* phylum during estrogen deficiency. Additionally, significant changes in the composition of the dominant intestinal microbiota were observed.[141]

Significant associations were identified between GM communities, particularly within the *Burkholderia* order, and an increase in osteoclasts, along with a reduced risk of PMO.[160] Studies have found that fecal samples collected from osteoporosis patients and healthy individuals show differences in the composition of the GM community, as analyzed by 16S rRNA gene sequencing. The results indicated that, at the phylum level, the *Aspergillus* and *Fusarium* groups were significantly more abundant in the osteoporosis (ON) group than in the normal control (NC) group, while the *Synergistic* group was significantly less abundant. At the genus level, *Roseburia, Clostridia_UCG.014, Agathobacter, Dialister*, and *Lactobacillus* showed significant differences between the OP and NC groups, as well as between the ON and NC groups. These findings suggest that gut flora dysregulation is associated with impaired host urate degradation and systemic inflammation, and could serve as a non-invasive diagnostic marker for gout.[161]

## Gout

The incidence of hyperuricemia (HUA) and gout continues to rise, representing a growing public health concern.[162] Studies have shown that alterations in the composition and metabolism of the GM lead to abnormal uric acid degradation, increased uric acid production, release of proinflammatory mediators, and impairment of the intestinal barrier, all of which contribute to the development of gout.[163]

A metagenomic analysis of 307 stool samples from 102 gout patients and 86 healthy controls revealed significant differences between the GM of gout patients and healthy controls. The relative abundance of *Prevotella, Fusobacterium*, and *Lactobacillus* was increased in gout patients, whereas *Enterobacteriaceae* and butyrate-producing bacteria were decreased[142] (Table 3). Additional studies have demonstrated bidirectional causality between the GM and host urate metabolism, with host-microbiota crosstalk playing a crucial role in patients with hyperuricemia. Alterations in the GM not only influence host urate metabolism but also serve as a prognostic indicator of urate metabolism disorders.[143,] Hyperuricemia, a precursor to gout, is commonly observed in other metabolic disorders associated with microbiota dysbiosis. A study analyzed the gut microbiota of hyperuricemic patients using 16S ribosomal RNA sequencing on fecal samples to assess microbial dysbiosis, including richness, diversity, composition, and the relative abundance of microbial taxa. The cohort consisted of 1,392 subjects (mean age 61.3 years, 57.4% female, 17.2% with hyperuricemia) from rural areas. Compared to patients with normouricemia, hyperuricemic patients exhibited reduced microbial abundance and diversity, altered microbiota composition, and a lower relative abundance of the genus *Synechococcus*.[164]

# Gut Microbiota and Cancer

Cancer metastasis is the leading cause of death among cancer patients. Recent studies have identified the intratumoral microbiota as an integral component of tumors, with evidence suggesting its functional regulation of various aspects of metastasis.[165] Tumor tissues from various origins harbor intratumoral microbial components, which are closely associated with cancer onset, progression, and therapeutic efficacy. The oral microbiota may contribute to cancer development and progression through mechanisms such as DNA mutations, activation of oncogenic pathways, promotion of chronic inflammation, modulation of the complement system, and facilitation of metastasis.[166] There is increasing evidence that the GM modulates the efficacy and toxicity of cancer therapies, particularly immunotherapy and its immune-related adverse effects. Adverse reactions to immunotherapy in patients receiving antibiotics further support the significant role of the microbiota.[167] Studies have identified 11 causal relationships between GM genetics and cancer, including one involving the genus *Bifidobacterium*. Additionally, 17 strong associations between genetic factors in the GM and cancer have been observed.[168] Imbalances in GM homeostasis have now been linked to several cancers.

## Lung Cancer

It has been demonstrated that the interaction between the human microbiota and lung cancer represents a complex, multifactorial relationship, with several pathways linking the microbiota, thereby supporting the existence of the gut-lung axis (GLA).[169] There are intricate communication pathways between the gut and lung microbiota, with this connection extending beyond the lymphatic and blood circulatory systems.[170] The lung microbiota can influence the composition and function of the GM via the blood circulation.[171] Aberrant activity of the GM is closely associated with the onset and progression of various respiratory diseases, including COPD, cystic fibrosis, respiratory infections, and asthma.[172] This suggests a bidirectional regulation of the gut-lung axis, indicating a complex biological interaction, with lung diseases often associated with intestinal dysbiosis and immune-inflammatory responses, where GM and its metabolites play a direct or indirect role in immune regulation.[173] Intratumoral injection of the butyrate-producing bacterium *Roseburia* promotes subcutaneous tumor growth, suggesting that the intratumoral microbiome may have potential prognostic and therapeutic value.[174] An increasing body of evidence suggests that the intratumoral microbiota may serve as diagnostic, prognostic, and therapeutic targets for emerging biomarkers.[175]

A 16S rRNA sequencing analysis of surgically resected tissue samples from patients with non-small cell lung cancer (NSCLC) and benign lung diseases revealed significant differences in the relative abundance of lung microbiota, as well as in α- and β-diversity between the two groups. At the genus level, significant differences in the abundance of 13 taxa

were observed between squamous cell carcinoma and adenocarcinoma of the lung.[180] Modulation of the intestinal microbiota has been shown to influence the anti-lung cancer response in mouse models, with the administration of probiotics and fecal microbiota transplants enhancing the effects of antitumor therapies. Supplementation with bacterial species, such as mucinophilic *Akkermansia*, which are known to be reduced in lung cancer patients, may offer a potential strategy to enhance the efficacy of these therapeutic interventions[176] (Table 4). The oral microbiota can be utilized in the prevention and treatment of lung cancer and to mitigate the side effects of anticancer therapies by modulating the balance of the oral microbiota.[181] Studies have shown that lung adenocarcinomas are enriched with Bacillus and Castorius, whereas lung squamous carcinoma is enriched with Brucella abortus. The microbial community is altered in patients with lung cancer, and its diversity may be associated with the disease site and pathology.[182] Overall, immune interactions within the gut-lung axis are bidirectional and complex, involving multiple interactions between the microbial components of both the intestinal and lung microbiota, with immune effects occurring both locally and distally. Disruptions in this axis may lead to adverse outcomes, including the promotion of cancer development, pathogen colonization, tissue damage, and increased susceptibility to infection.[170]

Microbial regulatory mechanisms offer novel opportunities for precision oncology in lung cancer. Tetrahydrobiopterin from Bacillus sp. SVD06 specifically induces apoptosis in human lung adenocarcinoma cells (A549).[183] Separately, RNase Binase secreted by Bacillus intermedius selectively targets A549 cells while triggering apoptosis programs, demonstrating negligible toxicity toward normal lung epithelial cells (LEK).[184] Notably, Coagulococcus species may influence chemotherapy resistance in lung adenocarcinoma by modulating DNA repair pathways.[185] In animal models, Wistar rats bearing synthetic squamous cell carcinomas maintain normal immune responses to sheep red blood cells and inactivated Brucella abortus during tumor progression. However, serum-detected immunosuppressive factors correlate with localized lymphocyte suppression and diminished antitumor immunity.[186]

## Breast Cancer

Advances in modern sequencing and metagenomics technologies have enabled a deeper understanding of the tumor microbiome, allowing for comprehensive characterization of tissues such as the breast. Breast cancer (BC) is the most common cancer among women and the leading cause of cancer-related deaths in women worldwide.[187] Mastitis is a condition characterized by engorgement, swelling, and inflammation of the mammary gland, typically resulting from infection by pathogenic microorganisms.[177] Emerging studies identify octamer-binding transcription factor 1 (OCT1) as a novel independent prognostic biomarker in estrogen receptor-positive breast cancer (ER+ BC).[188] Separately, poly (ADP-ribose) polymerase (PARP) inhibitors demonstrate favorable efficacy and safety in Phase I–II clinical trials for metastatic triple-negative breast cancer (TNBC) (Figure 4).[189]

A multi-omics analysis of triple-negative breast cancer (TNBC) patients revealed that Clostridiales spp. and the related metabolite trimethylamine N-oxide (TMAO) were more abundant in tumors with an activated immune microenvironment. TMAO induced a thermomorphic response in tumor cells through activation of the endoplasmic reticulum stress kinase PERK, thereby enhancing CD8+ T cell-mediated TNBC antitumor immunity in vivo (Figure 4).[190] The microbiota in the mammary gland differs between malignant tumors and normal tissues. Aerosolized antibiotics have been shown to reduce the growth of mammary tumors in mice and significantly limit lung metastasis. Oral absorbable

**Table 4** Gut Microbiota and Cancer

| Type | Relevancy | Changes in Intestinal Flora | References |
|---|---|---|---|
| Lung Cancer | Regulation of the gut microbiota has been shown to influence anti-lung cancer response in mouse models | Decrease in Akkermansia mucchiosin | [176] |
| Breast Cancer | Altered metabolic profiles of colon contents, plasma, and breast tissue | Increased abundance of Proteobacteria | [177] |
| Prostate Cancer | Bifidobacterium and Lactobacillus may be valuable in increasing the sensitivity of BCG to bladder cancer | Significant differences in the composition of the urinary microbiota | [178, 179] |

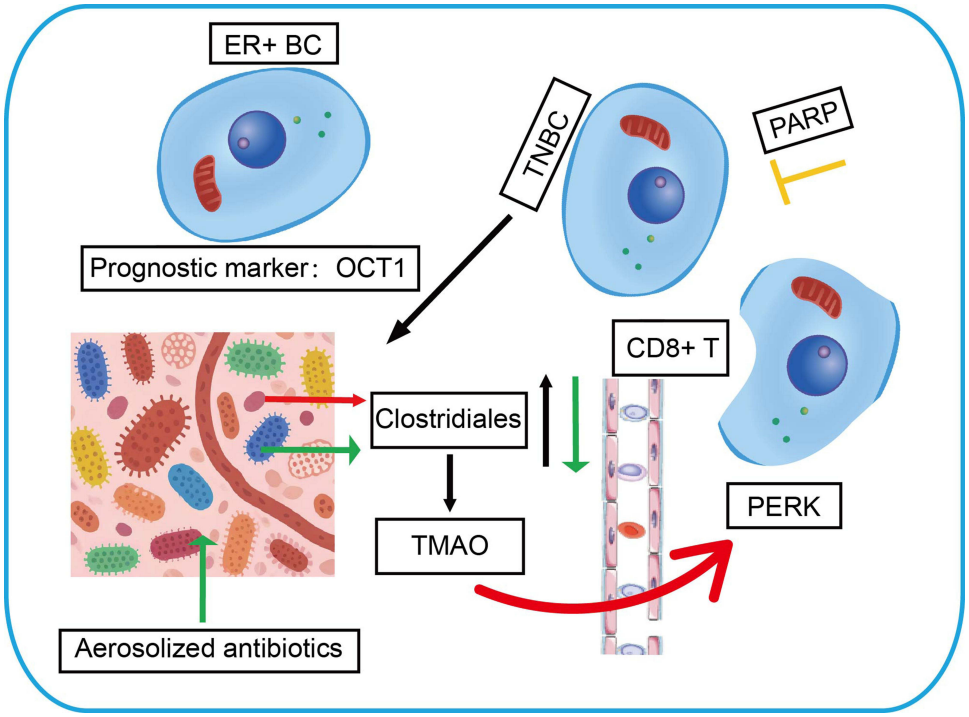


**Figure 4** In estrogen receptor-positive breast cancer ($ER^+$ BC), octamer-binding transcription factor 1 (OCT1) serves as a novel independent prognostic biomarker. Conversely, poly(ADP-ribose) polymerase (PARP) inhibitors demonstrate significant efficacy and safety in metastatic triple-negative breast cancer (TNBC). Notably, TNBC patients exhibit elevated gut Clostridiales abundance with increased circulating trimethylamine N-oxide (TMAO). Mechanistically, TMAO activates the PERK endoplasmic reticulum stress pathway, inducing tumor cell heat shock response and enhancing $CD8^+$ T cell-mediated anti-tumor immunity. Strikingly, oral broad-spectrum antibiotics suppress mammary tumor growth while reducing Clostridiales abundance, corroborating the causal role of gut microbiota in TNBC immunomodulation.

antibiotics also reduced mammary tumors. In ampicillin-treated nodes, the immune microenvironment exhibited M1 features and enhanced T-cell/macrophage infiltration.[191]

Some evidence suggests the presence of a unique microbial community in breast tissue, previously considered sterile. Additionally, breast tumors harbor distinct microbial communities that differ from those of normal breast tissue, and these microbial communities may originate from the gut microbiota.[187] A variety of factors can impact the gut microbiota, including, but not limited to, age, ethnicity, body mass index (BMI), physical activity level, dietary habits, concurrent medications, and antibiotic use.[192–194] For example, the abundance of mucinophilic *Akkermansia* increases with dietary shifts toward fiber-rich foods and has been correlated with body composition in some BC patients.[195] In addition, a prospective, randomized intervention trial conducted by Wastyk et al revealed a correlation between the intake of high-fiber or fermented foods and immune responses.[196] Enrichment in n-3 polyunsaturated fatty acids (PUFA) has been associated with a reduced risk of BC in offspring. Using C57BL/6 pregnant mice, it has been demonstrated that the alpha-diversity of the GM in n-3 Sup-FO and n-3 Sup-FSO offspring was significantly higher than that in n-3 Def offspring after maternal supplementation with n-3 PUFA. The relative abundance of Akkermansia, Lactobacillus, and Mucispirillum was observed to be higher in the n-3 Sup-FO and n-3 Sup-FSO offspring groups compared to the control group at all ages. Moreover, maternal n-3 Def diet was associated with reduced abundance of Lactobacillus, Bifidobacterium, and Pasteurella in the 7-week-old offspring. The n-3 Sup-FO and n-3 Sup-FSO groups were also found to be more diverse than the control group in the n-3 Sup-FO group.[197]

Dietary patterns modulate the mammary microbiota. Fecal transplantation has been shown to alter both the gut and mammary tumor microbiota, suggesting a link between the gut and mammary microbiota. Recent studies have demonstrated that high-density lipoprotein (HDL) cholesterol increases serum levels of bacterial lipopolysaccharides (LPS), and that fecal transplantation, controlling for dietary source, reduced LPS bioavailability in animals fed a high-fat diet (HFD).[198] A study revealed changes in the gut microbiota of mastitis rats, characterized by an increased abundance of the Aspergillus phylum. Mammary tissue showed elevated levels of arachidonic acid metabolites and norepinephrine. The

development of adenitis leads to changes in the microbiota and alterations in the metabolic profiles of various biological samples, including colon contents, plasma, and mammary tissue (Table 4). Major manifestations include disturbances in bile acid metabolism, amino acid metabolism, and arachidonic acid metabolism.[177]

## Prostate Cancer

Prostate cancer remains the most common non-cutaneous malignancy among male patients and one of the leading causes of cancer-related deaths worldwide. Increasing evidence suggests that the microbiota may play a crucial role in carcinogenesis and in modulating the efficacy and activity of anticancer therapies (eg, chemotherapy, immune checkpoint inhibitors, targeted therapies) across various hematologic and solid tumors.[199] Dysbiosis of the bladder microbiota has been linked to various urologic disorders.[200] Recent studies of the urinary microbiota have challenged the long-held belief that urine is sterile, as the urinary microbiota has been linked to the development of bladder and prostate cancers, similar to the role of the gut microbiota in cancer development.[201]

Using the inverse variance weighting or Wald ratio method, it was demonstrated that Bifidobacterium ($p = 0.030$), Actinobacterium (phylum $p = 0.037$, class $p = 0.041$), and Ruminococcus groups ($p = 0.018$) were associated with an increased risk of BCa, while Allisonella ($p = 0.004$, $p = 0.038$) was associated with a reduced risk of BCa and PCa, respectively.[178] Lactobacillus and Bifidobacterium probiotic mixtures enhanced the antitumor effects through the gut-tumor immune response axis[179] (Table 4). Compared to healthy controls, the urinary microbiota composition in patients with genitourinary cancers exhibited significant differences. Lactic acid-producing bacteria, such as *Bifidobacterium* spp. and *Lactobacillus* spp., may enhance the efficacy of Bacillus Calmette-Guerin (BCG) therapy in bladder cancer.

# Conclusion

Gut dysbiosis, as a cross-disease hub linking neurodegenerative disorders, psychiatric conditions, metabolic syndromes, and malignancies, demonstrates increasing clinical significance. In neurodegenerative contexts: Alzheimer's disease patients exhibit exacerbated amyloid-beta deposition via microglial inflammatory activation triggered by gut microbial metabolites; Parkinson's disease models reveal that enteropathic α-synuclein pathological dissemination precedes motor symptom onset, while microbiota-targeted interventions significantly alleviate neuroinflammation. Within psychiatric disorders: Depressed patients show reduced short-chain fatty acid SCFAs levels closely associated with hypothalamic-pituitary-adrenal (HPA) axis hyperactivity. Specific probiotics and natural compounds restore synaptic plasticity through gut-brain axis signaling repair. Metabolic disease research demonstrates: Diabetic patients' decreased butyrate-producing bacteria directly correlate with insulin resistance, with microbiota modulation strategies partially reversing glucose metabolic abnormalities. Regarding tumor microenvironment regulation: Gut microbiota influences immune checkpoint inhibitor efficacy through metabolic reprogramming, particularly demonstrating enhanced anti-tumor immunity potential in breast and triple-negative lung cancers.

At the metabolism-immune interface, microbial metabolites modulate systemic inflammatory states through receptor-mediated immunocyte differentiation. In neural signaling, enteropathic proteins influence central nervous functions via vagal nerve pathways. Regarding gut-brain axis regulation, microbial dysbiosis directly compromises intestinal barrier integrity, subsequently affecting distal organs through circulatory dissemination. These mechanisms reveal concerted multi-target effects of microbe-host interactions in disease pathogenesis. However, gut microbiota-disease interplay exhibits complex bidirectionality: Fecal microbiota transplantation (FMT) studies demonstrate that colonizing germ-free mice with patient-derived microbiota only partially recapitulates disease phenotypes, suggesting dysbiosis may represent a secondary outcome of genetic-environmental interactions. Longitudinal metabolomics profiling further reveals that altered tryptophan/kynurenine ratios during disease progression precede microbial structural shifts, implying host metabolic derangements may drive ecological remodeling of the microbiota.

# Outlook

Future gut microbiota research must transcend traditional correlative approaches by focusing on three innovation axes directly aligned with disease spectra: Firstly, developing spatiotemporal metabolite tracking technologies to precisely map real-time trajectories of effector molecules (eg, short-chain fatty acids, LPS) along the gut-brain axis signaling

pathway. This will capture organ-specific epigenetic imprints in neurodegenerative contexts—such as microglial activation in Alzheimer's disease and enteropathic α-synuclein dissemination in Parkinson's disease—and synaptic plasticity impairments in psychiatric disorders like depression. Secondly, constructing microbiota-host causal inference models through longitudinal metabolomic monitoring across the four disease dimensions. This approach will delineate temporal relationships between critical metabolic events—including tryptophan dysregulation in psychiatric disorders and insulin sensitivity modulation in metabolic diseases—and microbial structural shifts. It will further differentiate functional weights of driver strains (eg, checkpoint regulator microbes in malignancies) from commensal bacteria. Ultimately, advancing clinical translation of targeted interventions: Optimizing synthetic microbial community transplantation for disease-specific applications in neuroinflammation (Parkinson's models), metabolic dysregulation (diabetic insulin resistance), and tumor immunity (breast cancer estrogen metabolism); Engineering metabolite-directed delivery systems to restore intestinal barrier integrity (foundational for gut-brain axis repair in psychiatric disorders) while synergizing with vagal nerve pathways to improve neural function. This integrated strategy will enable precise ecological recalibration from "Microbial Homeostasis to Systemic Pathogenesis".

## Data Sharing Statement

The data analyzed in this review are derived from previously published studies, which are cited in the text. Readers are referred to the original publications for access to the data.

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## Disclosure

The authors declare that there are no competing interests associated with this work.

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