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The microbiome-mind connection: exploring gut health's impact on depression

Natalia Klepacz
Lower Silesian Center for Oncology, Pulmonology, and Hematology, Wrocław, Poland
https://orcid.org/0009-0007-7179-4601
Corresponding author: natklepacz@gmail.com

Aleksandra Rabęda
Independent Public Health Care Facility of the Ministry of Internal Affairs and Administration, Kraków, Poland
https://orcid.org/0009-0008-1701-6494

Karina Grzesik
T. Marciniak Lower Silesian Specialist Hospital – Center of Emergency Medicine, Wrocław, Poland
https://orcid.org/0009-0006-1362-8843

Katarzyna Pilarczyk
T. Marciniak Lower Silesian Specialist Hospital – Center of Emergency Medicine, Wrocław, Poland
https://orcid.org/0009-0002-4942-3656

Hanna Adamska
T. Marciniak Lower Silesian Specialist Hospital – Center of Emergency Medicine, Wrocław, Poland
https://orcid.org/0009-0007-1338-1382

Marta Kaus
Lower Silesian Center of Oncology, Pulmonology and Hematology in Wrocław, Wrocław, Poland
https://orcid.org/0009-0004-3935-0304

Weronika Ewa Nowak
Jan Mikulicz-Radecki University Clinical Hospital, Wrocław, Poland
https://orcid.org/0009-0006-8445-2072

Hubert Sawczuk
Jan Mikulicz-Radecki University Clinical Hospital, Wrocław, Poland
https://orcid.org/0009-0003-2860-9002

Zuzanna Cudziło
Jan Mikulicz-Radecki University Clinical Hospital, Wrocław, Poland
https://orcid.org/0009-0000-9666-3156

Marta Malicka
Jan Mikulicz-Radecki University Clinical Hospital, Wrocław, Poland
https://orcid.org/0009-0009-1955-6512

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ABSTRACT

Introduction. The gut-brain axis is considered to be a crucial component of mental health, significantly influenced by the gut microbiota. This axis operates through neural (vagal nerve), hormonal (Hypothalamic-Pituitary-Adrenal axis), and immune pathways. Key mechanisms include microbial production of neurotransmitters like serotonin and gamma-aminobutyric acid, modulation of inflammatory responses and metabolic pathways involving short-chain fatty acids. Dysbiosis - a microbial imbalance - is associated with increased inflammation and neurotransmitter disruptions, both contributing to depressive symptoms.
Material and methods. The search strategy was centered on gathering high-quality articles focusing on the gut-brain axis and its implications for mental health, particularly depression. Databases including PubMed,

Scopus, and Google Scholar were searched using keywords such as "gut-brain axis," "microbiota and mental health," "depression and gut microbiome," "gut neurotransmitters," "probiotics," and "inflammation and mood disorders." Studies were selected with a focus on research published mainly within the last two years.
Results. Potential interventions, such as administration of probiotics, prebiotics, dietary modifications, and innovative therapies like fecal microbiota transplantation and vagus nerve stimulation intend to restore the gut microbiota equilibrium.
Conclusions. Despite the limitations of current research, such as reliance on animal models, small human sample sizes, and methodological inconsistencies, expanding these studies remains highly valuable. Conducting large-scale human trials with standardized protocols and deeper exploring the interactions of specific microbial species could create a foundation for new approaches to supporting the treatment of depression effectively.

Introduction to Human Microbiota

The human gastrointestinal (GI) tract, particularly the intestines, hosts a vast array of microorganisms, predominantly bacteria, alongside smaller populations of viruses, fungi, and archaea. The largest concentration of these microorganisms reside in the colon, where they form a complex microbial community that interacts with the host, influencing a range of physiological and pathological processes.

The bacterial composition of the gut microbiota is dominated by *Firmicutes* and *Bacteroidetes phyla*, although *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia* are also present in smaller proportions, contributing to its diversity and functionality [1].

Development of Gut Microbiota

The development of the gut microbiota begins at birth and undergoes significant changes during infancy and early childhood [2]. Factors shaping this dynamic process include:

- Mode of Delivery: Vaginally delivered infants acquire a microbiota resembling the maternal vaginal flora, whereas those born by cesarean section show microbiota patterns more similar to the maternal skin microbiome [3].
- Diet: Breastfeeding supports a distinct microbiota profile, with bacteria like *Bifidobacterium*. Formula feeding, however, leads to a more diverse microbiota composition, resembling that of adults [4]. While such diversity is generally considered beneficial in older children and adults, in infants, it may not offer the same immune-protective benefits as a bifidobacteria-dominant profile.
- Environmental Exposures: Both prenatal and postnatal antibiotic exposure can disrupt microbial colonization, increasing the risk of metabolic and allergic diseases later in life [5]. Antibiotics interfere with the passing of beneficial bacteria from mother to child, causing reduced microbial diversity and imbalance in species.

Geographic and Dietary Influences on Gut Microbiota Composition

Geographic factors, especially regional dietary habits, significantly impact the diversity and structure of the gut microbiota. Western diet pattern, rich in fats and proteins, is associated with an increase in the *Bacteroides* enterotype and generally contributes to lower microbial diversity. In contrast, fiber-rich diets common in non-Western countries are typically associated with higher levels of *Prevotella*, a genus linked to carbohydrate-rich, plant-based diets [6].

Polyphenols are found abundantly in plant-based foods such as fruits, vegetables, tea, wine, and cocoa. Due to their prebiotic-like properties, polyphenols bypass digestion in the small intestine and reach the colon, where they serve as a nutrients for beneficial microbes, thereby enhancing microbiota composition [7].

Within individual countries, urbanization also affects gut microbiota diversity. Rural populations, who often maintain traditional diets rich in fiber and low in processed foods, display higher microbial diversity than urban populations, whose diets tend to be abundant in processed and fat-dense foods. Another impacting element is seasonal dietary variations and lifestyle. For example, rural populations in Mongolia demonstrate

seasonal shifts in microbiota composition due to changes in available food sources, supporting a microbiota that is both diverse and adaptable [6].

Functional Roles of Gut Microbiota

The gut microbiota plays various essential roles in maintaining host health, acting as a metabolic, immunologic, and protective barrier. Key functions include:

- Metabolic Functions: The gut microbiota ferments dietary fibers to produce short-chain fatty acids (SCFAs) like butyrate, acetate, and propionate. These SCFAs serve as an energy source for colon cells and help regulate glucose and lipid metabolism [8]. Unlike other cells that primarily use glucose, colonocytes rely on SCFAs to produce ATP through the citric acid cycle [9].
- Immune Modulation: The microbiota influences both the innate and adaptive immune responses [10]. Microbial products and metabolites stimulate immune cells - including macrophages, dendritic cells, and neutrophils - enhancing their ability to recognize pathogens and modulate inflammatory responses. Certain bacterial species also contribute to the development of T helper 17 (Th17) cells and the differentiation of T regulatory cells (Tregs). One pathway through which these bacteria exert their influence is by conjugating bile acids. Preclinical experimental studies in mice have demonstrated that this conjugation significantly impacts the intestinal microbiota, thereby promoting the differentiation of Th17 and Treg cells [9].
- Barrier Integrity and Defense: The gut microbiota competes with pathogenic organisms for resources and attachment sites, thereby preventing colonization by pathogens. It strengthens gut epithelial integrity by enhancing tight junctions and occupies binding sites along the intestinal lining, blocking pathogens from attaching [11, 12].

Dysbiosis and Disease Associations

Disruptions in the composition of microbiota - known as dysbiosis - are increasingly associated with various disease states:

- Metabolic Disorders: Alterations in gut microbiota composition are associated with metabolic diseases, including obesity, type 2 diabetes, and non-alcoholic fatty liver disease [13].
- Gastrointestinal Diseases: The intestinal microbiota supports nutrient absorption, maintains gut barrier integrity, and contributes to peristaltic movement, facilitating efficient digestion [14]. Dysbiosis has been associated with inflammatory bowel diseases, irritable bowel syndrome (IBS), and other gastrointestinal disorders [15].
- Immune-Related Diseases: Altered microbiome has been linked with immune dysregulation, which can predispose to conditions such as allergies, asthma, and autoimmune diseases [16].
- Neurological and neuropsychiatric Disorders: Dysbiosis has been connected to mood disorders such as anxiety and depression, as well as to attention deficit hyperactivity disorder [17], Parkinson's disease, and Alzheimer's disease [18].

The following section will explore the mechanisms underlying these interactions, highlighting how gut health influences neurological and psychological outcomes.

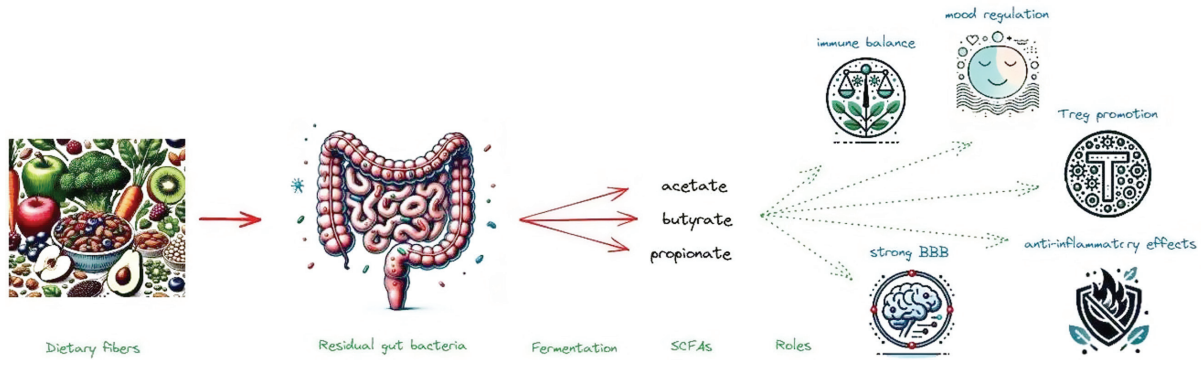

Figure 1. The pathway of SCFAs formation and their role in maintaining health.

Gut-Brain Axis: Pathways of Interaction

The gut-brain axis is a complex, bidirectional communication system between the central nervous system (CNS) and the gastrointestinal tract. The key pathways are mediated by neural (particularly the vagus nerve), hormonal, and immunological routes. Each one contributes uniquely to the intricate dialogue between the gut and the brain, helping regulate functions from digestion and mood to immune responses and cognition.

Vagus Nerve Pathway

The vagus nerve transmits critical information from the GI tract to the brain via neurotransmitters such as serotonin, dopamine, gamma-aminobutyric acid (GABA), and acetylcholine, each of which influences mood, stress responses, and overall mental health [19].

Approximately 90% of the body's serotonin is synthesized in the gut by enterochromaffin cells, a process profoundly influenced by microbial metabolites [20]. While gut-derived serotonin does not cross the blood-brain barrier, it modulates mood and emotional states indirectly through vagal signaling, ultimately affecting central serotonergic neurons [21]. Gut bacteria also play a role in serotonin production by synthesizing its precursor - tryptophan, with species like *Bacteroides* regulating its availability and conversion [22]. Short-chain fatty acids contribute to the promotion of serotonin release [23].

Certain gut bacteria, particularly strains of *Lactobacillus* and *Bifidobacterium*, convert glutamate to gamma-aminobutyric acid, an inhibitory neurotransmitter essential for reducing neuronal excitability and regulating anxiety [24]. When gut-derived GABA binds to vagal receptors, it76y triggers excitatory pathways that signal to the brainstem, specifically affecting areas such as the locus coeruleus and hypothalamus, demonstrating promising anxiolytic effects [23, 25]. For example, *Lacticaseibacillus rhamnosus* has been shown to alter GABA receptor expression in the prefrontal cortex, impacting mood and behavior [26]. In a study by Strandwitz, GABA- producing bacteria were linked to reduced anxiety-like behaviors in mice. Introducing these bacteria into germ-free mice increased brain GABA levels and reduced stress-induced hyperactivity [27].

Short-chain fatty acids synthesized by bacteria like *Clostridium butyricum* and *Bacteroides thetaiotaomicron* can influence dopaminergic pathways via vagal signaling, potentially impacting reward-related brain regions. In a study by Dalile et al., healthy participants received a mixture of SCFAs (acetate, propionate, and butyrate), which modulated activity in brain regions associated with reward and motivation, particularly the nucleus accumbens [28]. SCFAs interact with G-protein-coupled receptors (GPCRs) such as GPR41 and GPR43, which are expressed on enteroendocrine cells and vagal afferent neurons. Activation of these receptors by SCFAs can modulate the release of gut hormones like peptide YY and glucagon-like peptide-1, which in turn influence brain function [29].

Although most dopamine in the CNS is synthesized locally, gut-derived dopamine affects local GI functions and systemic signaling rather than directly modulating CNS dopamine levels. It interacts with D1-D5 dopamine receptors, where signaling through D2, D3 and D4 receptors influences the release of acetylocholine and vasoactive intestinal peptide [30]. While these effects have been observed primarily in animal models, further research is necessary to confirm these mechanisms in human studies [31]. Some bacterial strains, including *Lacticaseibacillus rhamnosus* and Limosilactobacillus reuteri, influence acetylcholine release, stimulating the vagus nerve to activate the cholinergic anti-inflammatory pathway. Acetylcholine binds to nicotinic acetylcholine receptors located on immune cells like macrophages [31]. This pathway reduces pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), contributing to systemic inflammation control [1, 32]. The vagus nerve pathway illustrates how gut-derived neurotransmitters, microbial metabolites, and specific bacterial strains influence CNS function and mental health. While serotonin and dopamine from the gut influence brain function indirectly, others, such as GABA and SCFAs, have direct impacts on neural signaling and neuroinflammation.

Hormonal Pathway (Hypothalamic-Pituitary-Adrenal Axis)

The Hypothalamic-Pituitary-Adrenal (HPA) axis is a key hormonal pathway in the gut-brain axis, par-

ticularly relevant to stress responses. When physical or psychological stressors activate the HPA axis, it initiates a cascade that begins with the release of corticotropin-releasing hormone (CRH) from the hypothalamus, stimulating the pituitary gland to secrete adrenocorticotropic hormone (ACTH). ACTH then acts on the adrenal glands, prompting the release of cortisol, a glucocorticoid that modulates immune function, mobilizes energy, and helps maintain homeostasis [33].

SCFAs can influence HPA axis activity indirectly by modulating cortisol production, enhancing immune responses, and supporting the integrity of the blood-brain barrier - all factors that contribute to stress resilience [29, 34]. Additionally, SCFAs promote the production of regulatory T-cells, which help stabilize immune responses [28].

Beyond SCFAs, gut bacteria also affect HPA axis through tryptophan metabolism. Tryptophan, an essential amino acid from dietary sources, can follow one of two primary metabolic pathways: conversion to serotonin or to kynurenine, with the direction depending on immune conditions. In states of chronic inflammation, tryptophan is more likely to be metabolized into kynurenine, which activates the HPA axis and promotes cortisol release. Elevated kynurenine levels have been associated with mood and stress-related disorders [19].

Certain probiotic strains, such as *Bifidobacterium longum* and *Lacticaseibacillus rhamnosus*, have shown potential in modulating HPA axis activity. Studies on *Lacticaseibacillus rhamnosus* indicate its ability to lower corticosterone levels and alleviate anxiety-like behaviors. These findings align with research showing that *Lacticaseibacillus rhamnosus* affects GABA signaling through the vagus nerve, highlighting its role in regulating both neurotransmitters and hormones [26, 35].

The HPA axis indicates that through the modulation of cortisol production and tryptophan metabolism, gut microbiota may significantly impact mental health and stress resilience [18].

Immunological Pathway

The immune system plays a significant role in gut-brain communication, as changes in the microbiota can modify immune responses, potentially triggering inflammation and neurobiological alternations [36].

Dysbiosis can increase intestinal permeability, allowing endotoxins such as lipopolysaccharides (LPS) from Gram-negative bacteria to enter the bloodstream. LPS can trigger systemic inflammation and, once crossing the blood-brain barrier (BBB), may lead to neuroinflammation and contribute to neurological and neuropsychiatric disorders [36, 37].

An imbalanced microbiota can overstimulate immune cells, resulting in the release of pro-inflammatory cytokines, including IL-6, TNF-α, and interleukin-1 beta (IL-1β), which reach brain through vagus nerve or by crossing BBB [38].

Microglia, the resident immune cells of the central nervous system, play a critical role in responding to injury and maintaining brain health. However, when overactivated by signals from peripheral inflammation, often due to gut dysbiosis, microglia can become neurotoxic, disrupting synaptic function [39].

The immunological pathway shows how gut dysbiosis and immune dysregulation drive neuroinflammation, emphasizing the role of beneficial bacteria in maintaining balance.

Gut Microbiota Influence on Depression

While the gut-brain axis has broad implications for neurological and mental health, depression repre-

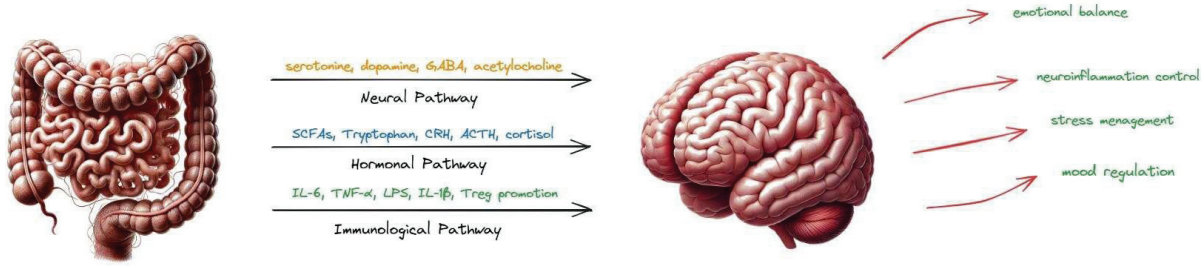

Figure 2. Key pathways in Gut-Brain axis and the main components contributing in each.

sents an area where microbial interventions hold particular promise. By examining neurotransmitter synthesis, immune modulation, and metabolic pathways, we can gain a clearer understanding of how gut microbiota might interact with and potentially reduce depressive symptoms.

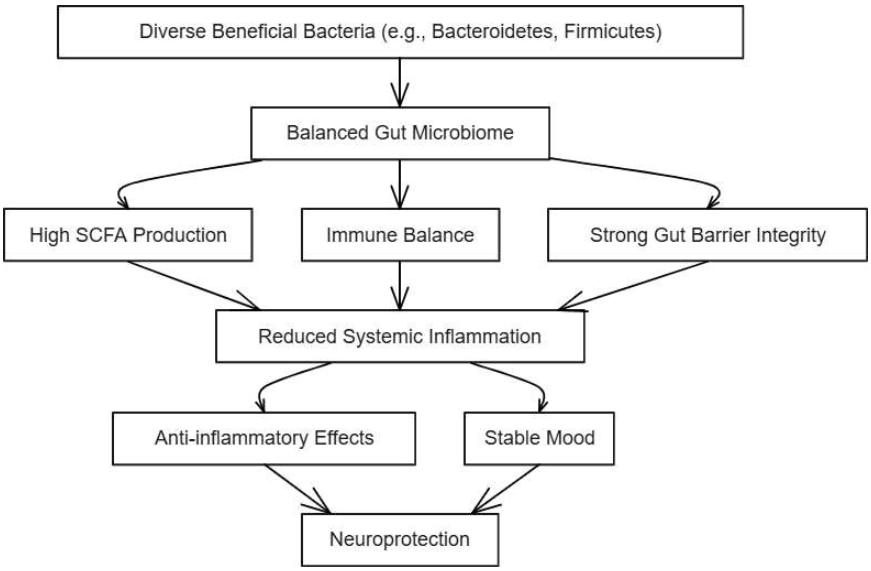

Figure 3. Influence of the balanced gut microbiota on the nervous system.

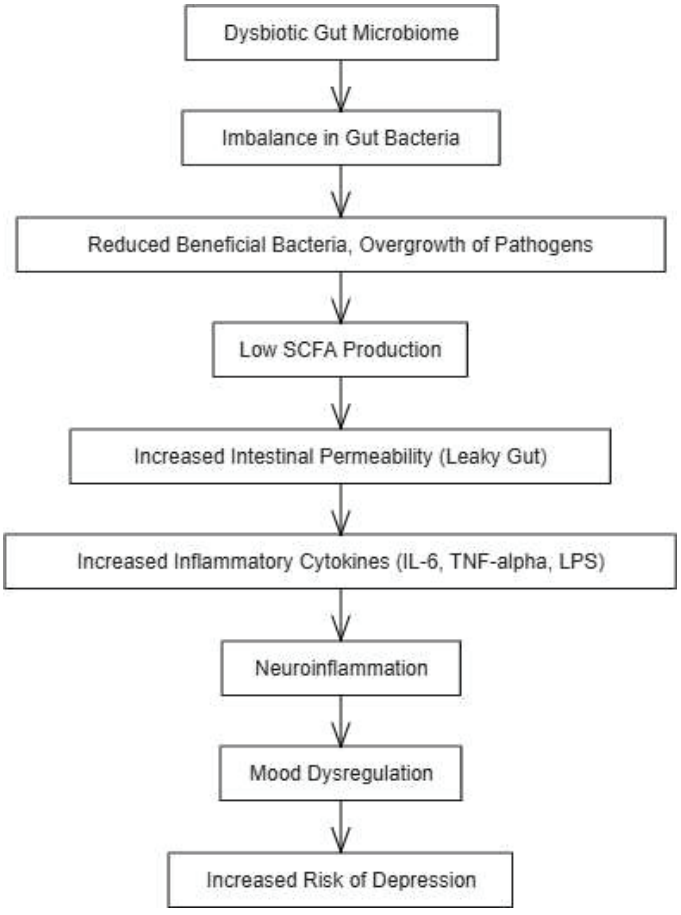

Figure 4. Influence of the imbalanced microbiota on the nervous system.

Neurotransmitter Production and Depression

As previously discussed, neurotransmitter production in the gut is crucial for maintaining CNS function. In the context of depression, neurotransmitters like serotonin, dopamine, and gamma-aminobutyric acid are essential for mood regulation. The shikimate pathway is worth mentioning. It is a crucial metabolic route found in bacteria, fungi, algae, and plants. It begins with simple carbohydrate precursors and proceeds through seven enzymatic steps, ultimately leading to the formation of chorismate. This compound is further converted into aromatic amino acids, which are vital precursors for the production of the mentioned neurotransmitters [40].

Research has demonstrated that certain bacterial strains, such as *Lacticaseibacillus paracasei*, enhance serotonin production, alleviating depressive symptoms related to gastrointestinal distress [41]. This effect is facilitated by increased tryptophan uptake in the gut. In a randomized clinical trial Peijun Tian demonstrated that *Bifidobacterium* breve CCFM1025 decreased major depressive disorder (MDD) by modulating gut microbiome composition and tryptophan metabolism [42]. In people with MDD, tryptophan is often shifted more toward the kynurenine pathway, leading to metabolites that can contribute to neuroinflammation and neurotoxicity.

Bifidobacterium breve CCFM1025 might reduce this switch, promoting a healthier balance by favoring serotonin production over kynurenine pathway metabolites [42].

Studies on germ-free animal models show that the absence of *Lactobacillus* and *Bifidobacterium* species can lead to lower levels of serotonin and dopamine, which may be partially restored through microbial reconstitution [43, 44]. Another compelling piece of evidence linking neurotransmitter levels and depression is the study conducted by Wu, which used chronic restraint stress (CRS) in mice as a depression model. These mice exhibited classical

depressive-like behaviors. Compared to the control group, the depressed mice demonstrated significantly decreased levels of norepinephrine, 5-hydroxyindoleacetic acid (5-HIAA), and serotonin (5-HT) in the hypothalamus, underscoring the critical role of neurotransmitter dysregulation in the pathophysiology of depression [45].

Immune System Modulation in Depressive Pathways

As noted earlier, lipopolysaccharides can enter the bloodstream, triggering systemic inflammation. LPS binds to Toll-like receptor 4 which activates a signaling cascade, ultimately stimulating the production of pro-inflammatory cytokines and inflammatory mediators [46].

Elevated levels of interleukin-6 and tumor necrosis factor-alpha have been associated with depressive symptoms due to their neuroinflammatory effects upon crossing the blood-brain barrier [47, 48].

Chronic inflammation is a hallmark of MDD and studies show that dysbiosis-driven inflammation stimulates microglial activation in the brain [43]. Overactive microglia release further pro-inflammatory mediators, disrupting neuronal function and synaptic plasticity, contributing to neurodegenerative and neuropsychiatric disorders [49]. Certain probiotics, such as *Lacticaseibacillus rhamnosus* and *Bifidobacterium longum*, have demonstrated efficacy in reducing inflammation by restoring gut barrier function and decreasing the levels of pro- inflammatory cytokines [41, 50].

Metabolic Pathways and Short-Chain Fatty Acids in Depression

The metabolic impact of gut microbiota on depression is largely mediated through SCFAs. Butyrate, in particular, is recognized for its neuroprotective and anti-inflammatory properties, supporting mood stabilization by reducing neuroinflammation and strengthening the blood-brain barrier [47]. SCFAs bind to G-protein-coupled receptors (GPCRs) like GPR41 and GPR43 on immune cells, leading to decreased production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, while enhancing the secretion of anti-inflammatory cytokines like IL-10. Qi Xu in his research linked SCFAs downregulating function to the NOD-like receptor protein 3 inflammasome, a critical driver of neuroinflammation in the hippocampus, to the alleviation of depression-like behaviors in mouse models [51].

Zeng and Tang also investigated the impact of SCFAs on psychiatric symptoms in individuals during the COVID-19 pandemic. Their findings indicated a reduction in depression and anxiety

levels, which correlated with an increased presence of SCFA-producing bacteria [52].

Clinical Implications and Practical Therapeutic Approaches for Depression

Given the growing understanding of the gut-brain axis, several therapeutic approaches target gut microbiota to manage depression. These strategies include probiotics, prebiotics, dietary interventions, and emerging techniques such as vagus nerve stimulation and fecal microbiota transplantation.

Probiotics and Prebiotics in Depression Management

As previously discussed, probiotics and prebiotics show promise in modulating the gut-brain axis [53]. Specific strains, including *Lacticaseibacillus rhamnosus* and *Bifidobacterium longum*, have been associated mood improvement, likely due to their roles in neurotransmitter synthesis and immune modulation [41, 50]. Prebiotics, that stimulate SCFA production, further enhance this process by stabilizing immune responses and supporting overall mental health.

These probiotics have shown significant benefits in reducing both gastrointestinal symptoms and depressive symptoms in IBS patients [54]. In Sanjay Noonan's review, probiotic supplementation significantly reduced depressive symptoms, as measured by scales like Hamilton Depression Rating Scale (HAM-D) and Beck Depression Inventory (BDI) [55]. Furthermore, probiotics were noted to enhance the effects of conventional antidepressants, suggesting potential as an adjunctive therapy. This additive effect may result from probiotics' ability to modulate systemic inflammation and improve the overall gut environment, which positively affects brain function.

However, the review also points out that the beneficial effects were often temporal, with symptoms reappearing after cessation of probiotic use.

In a randomized clinical trial 110 patients with MDD were assigned to one of three groups: probiotic supplementation (*Lactobacillus helveticus* and *Bifidobacterium longum*), prebiotic supplementation (galactooligosaccharide), or placebo [56]. After 8 weeks of intervention the results in BDI scores and changes in kynurenine/tryptophan and tryptophan/branched-chain amino acids (BCAAs) ratios were taken. The probiotic group exhibited a significant reduction in BDI scores (from 18.25 to 9.0), compared to the placebo group (18.74 to 15.55) and the prebiotic group (19.43 to 14.14). While no significant differences were observed between groups in kynurenine/tryptophan and tryptophan/BCAA ratios, the probiotic group showed a significant decrease in the kynurenine/tryptophan ratio after adjusting for serum isoleucine levels.

The arising field of personalized medicine uses microbiome profiling to tailor treatments based on an individual's unique microbial composition. Studies explored the use of personalized probiotics based on individual microbiome profiles to treat depressive symptoms [57].

Researchers conducted a clinical trial involving patients with MDD, who received a customized probiotic regimen tailored to their specific microbiome composition. By customizing therapies to the individual microbiome profiles, personalized medicine can optimize microbial balance, reduce inflammation, and enhance neurotransmitter synthesis, thereby alleviating depressive symptoms. However, the limited effects observed with prebiotics and mixed results regarding metabolic markers underscore the complex relationship between diet, microbiota, and mental health. In the future, with standardized treatment protocols in place, routine gut microbiota diagnostics for patients with depression undergoing psychiatric treatment may become a standard practice, allowing for the selection of appropriate probiotics to support the primary treatment of the disease.

Dietary Interventions and Depression

Dietary modifications are a non-invasive approach to enhancing gut microbiota balance and improving mental health. The Mediterranean diet, known for its anti-inflammatory effects, and the low-FODMAP diet, which reduces fermentable carbohydrates, have both shown potential in alleviating depressive symptoms by promoting SCFA production and reducing gut inflammation [50, 58]. The Mediterranean diet is rich in fruits, vegetables, whole grains, nuts, seeds, olive oil, and moderate amounts of fish and poultry - foods high in fiber and polyphenols. While the low-FOD-

MAP diet is mainly used to manage symptoms of irritable bowel syndrome, emerging research suggests its potential to alleviate depression-related symptoms. Although low-FODMAP diet tends to reduce overall microbial diversity, it also selectively decreases the abundance of certain gas-producing bacteria, potentially easing GI symptoms and inflammation.

In a randomized clinical trial, Stilling demonstrated that increasing dietary fiber intake correlates with improved markers of neuroinflammation and microglial function in older adults [9].

Participants who consumed more fiber had higher levels of SCFAs, which were linked to reduced expression of inflammatory cytokines and microglial overactivity in brain imaging studies. These dietary interventions offer accessible strategies to improve microbiota composition and, in turn, support mood regulation [59]. Additionally, a study by Tončić observed that diet approaches promoting SCFA production were associated with sustained improvements in mood over time [47].

In clinical studies, such as the "SMILES" trial, participants with major depressive disorder who followed a modified Mediterranean diet (ModiMedDiet) experienced significant reductions in depressive symptoms, along with lower cortisol levels and improved stress resilience. After 12 weeks, participants in the dietary group showed a notable decrease in their Montgomery–Åsberg Depression Rating Scale (MADRS) scores, from 26.1 at baseline to 14.8, highlighting the potential of the Mediterranean diet as an adjunctive therapy for depression [60].

Diets high in polyunsaturated fatty acids (PUFA), particularly omega-3 fatty acids from fish, have been associated with lower depressive symptom scores. Participants following a Mediterranean diet supplemented with omega-3 PUFAs reported a 45% reduction in depression scores, compared to a 26.8% reduction in the control group [61].

Similar findings were observed in the comparison of 17 randomized controlled trials on the role of dietary interventions, particularly in relation to depression and anxiety, as presented in the work of Rachelle S. Opie [62]. In this study, outcomes were measured using the Beck Depression Inventory and the Hospital Anxiety and Depression Scale (HADS), revealing that approximately 47% of the studies reported a significant reduction in depressive symptoms in the intervention groups. Notably, interventions focusing on Mediterranean diets or increasing polyunsaturated fatty acids were more likely to yield positive results. These findings underscore the interplay between diet, microbiota, and hormonal balance, suggesting new avenues for managing depression [63]. Given these studies, it would be beneficial for clinicians to implement the Mediterranean diet for patients with depression. Such a diet should include a high intake of fruits, vegetables, whole grains, nuts, seeds, olive oil, and moderate amounts of fish and poultry. Mentioned foods are rich in fiber, polyphenols, and omega-3 fatty acids, which can help improve gut microbiota balance and support mental health. Clinicians may consider collaborating with dietitians to create personalized dietary plans for patients, ensuring optimal nutritional support for the treatment of depression [64].

Vagus nerve stimulation and Depression

Vagus nerve stimulation (VNS) has emerged as a promising intervention for treating both psychiatric and gastrointestinal conditions, reflecting its role in the gut-brain axis. Initially approved for epilepsy, VNS has shown effectiveness in treating treatment-resistant depression. This neuromodulatory therapy works by modulating the autonomic nervous system, reducing sympathetic activity, and enhancing parasympathetic tone. Applied modulation results in decreased inflammation and improved autonomic control of the GI tract [65]. This dual efficacy highlights the interconnected nature of psychiatric and GI symptoms mediated through the vagus nerve [66]. A systematic review by Guerriero evaluated the efficacy of transcutaneous vagus nerve stimulation (tVNS) for treating depression, revealing significant improvements in mood and anxiety levels [67]. Similarly, a clinical trial by Shi demonstrated that transcutaneous auricular vagus nerve stimulation reduced symptoms of functional dyspepsia while also easing depression- related effects [68]. Clinical applications of VNS also have shown marked improvements in patients suffering from IBS experiencing concurrent mood disorders - patients undergoing VNS reported both a decrease in GI discomfort and an enhanced mood stability.

Fecal microbiota Transplantation and Depression

Fecal microbiota transplantation (FMT), based on the transfer of a healthy donor's gut microbiota to a recipient, aims to alter the recipient's microbiome to confer health benefits. The procedure's goal is to optimize the complex bidirectional communication between the gut microbiota and the central nervous system [58].

In a clinical trial conducted by Zhang, 18 patients with irritable bowel syndrome and mild to moderate symptoms of depression and anxiety were divided into two groups: one receiving fecal microbiota transplantation and a control group [69]. The FMT group demonstrated marked improvements in both gastrointestinal symptoms and mental health parameters (Quality of Life measures and Gastrointestinal Symptom Rating Scale). Post-treatment analysis revealed significant reductions in levels of isovaleric and valeric acids, as well as notable changes in gut bacterial profiles. Similar conclusions have been reached by Kurkowa in her study, where 17 patients with Functional Gastrointestinal Disorders (FGIDs) were observed after undergoing FMT therapy [70]. At baseline, 12 out of 17 patients had a HAM-D score of 8 or higher, indicating notable depressive symptoms. After treatment, patients experienced significant improvements in scores for depression (HAM-D), anxiety (HAM-A), and quality of life - all with statistically meaningful results.

Acupuncture in Depression

Acupuncture is increasingly recognized as a complementary therapy for depression, valued for its therapeutic effects and minimal side effects, which have garnered global research interest.

Acupuncture has been shown to decrease levels of pro-inflammatory cytokines in the gastrointestinal tract, potentially reducing systemic inflammation linked to depressive symptoms. Additionally, this procedure may shift gut microbiota composition by promoting populations of beneficial bacteria [71]. Hiang-Yun Yan study aimed to evaluate the effect of acupuncture on gut microbiota in 80 patients with functional constipation and 28 healthy controls [72]. The composition and predictive metabolic function of the gut microbiota from fecal samples were analyzed using 16S rRNA gene sequencing, while fecal SCFAs were identified via gas chromatography-mass spectrometry (GC-MS). Results showed that acupuncture restored the composition of gut microbiota. Specifically, the abundance of beneficial bacteria such as *Lactobacillus* increased, while that of pathogenic bacteria like *Pseudomonas* decreased. These changes were significantly correlated with alleviated constipation symptoms. Additionally, ten microbes, including *Lactobacillus* and *Eubacterium* coprostanoligenes group, were identified as acupuncture-specific microbes and formed a stable interaction network. Research on animal models of depression has shown that acupuncture, by interacting with the brain-gut axis, can improve this communication and help balance neurotransmitter levels, such as serotonin and dopamine [73]. Acupuncture supports the regulation of gut microbial homeostasis, reduced intestinal inflammation by lowering pro- inflammatory cytokines, and enhanced intestinal barrier function by increasing the expression of tight junction proteins. These combined effects contribute to enhanced communication between the gut and brain, mediated through the vagus nerve [74]. Although acupuncture has demonstrated favorable results, limitations include the need for consistent methodology in terms of dosage and points of stimulation across studies.

Limitations of Current Research

While existing studies provide valuable insights, there are several limitations. Key areas of concern include the reliance on animal models, methodological variability, and individual differences in microbiome composition. It highlight the need for further standardization and more extensive human trials to confirm findings and improve therapeutic potential.

First, most research relies on animal models, limiting the direct applicability of findings to human physiology. For instance, studies examining the anti-inflammatory effects of short-chain fatty acids on the brain often use animal models and translating these findings to human applications remains uncertain due to physiological variances in SCFA pathways. Further, while germ-free mice models have shown a correlation between certain microbiota and behavioral changes, these

models do not fully replicate human complexity, limiting the robustness of the findings.

Moreover, studies that include human participants often suffer from small sample sizes and lack longitudinal data, which weakens the ability to understand long-term effects and causal relationships. For example, while FMT and VNS have demonstrated short-term improvements in clinical symptoms, the lack of long-term follow-up studies means the durability of these benefits remains unclear. Individual variability in gut microbiota composition significantly impacts therapeutic outcomes, underscoring the need for precision medicine approaches tailored to individual microbiome profiles. For example FMT outcomes depend heavily on donor microbiome quality. Diversity in microbiome responses to interventions such as probiotics and dietary changes has also been observed, suggesting that personalized treatments may be essential for effective long-term management.

Additionally, there is significant variability in methodologies, such as differences in dietary interventions, strains of probiotics used, and biomarkers measured, which complicates comparison across studies. For instance, studies on probiotics often use different bacterial strains, such as *Lacticaseibacillus rhamnosus* in some trials and *Bifidobacterium longum* in others. The field would benefit from standardizing protocols for interventions like FMT, VNS, and probiotic administration. Establishing standardized protocols could enhance the comparability and reproducibility of studies, allowing researchers to better evaluate the efficacy and safety of these treatments. To mitigate current limitations, future research should incorporate multi-omics approaches, which integrate wide data to provide a comprehensive understanding of microbiome functions and interactions [75]. Furthermore, larger sample sizes and longitudinal studies seem to be essential to capture the variability and long-term effects of microbiome interventions. [76].

Collaborative efforts across research institutions could help standardize methodologies and protocols, ensuring consistency and reliability in findings. By addressing these limitations, the field can advance towards more effective and personalized microbiome - based therapies.

Conclusions

The reviewed literature on the gut-brain axis clarifies its complex, bidirectional communication pathways involving neural, hormonal, and immunological mechanisms. This axis, significantly impacted by gut microbiota, mediates critical physiological processes, that influence both gastrointestinal and central nervous system health. It should be kept in mind that the gut microbiota represents a promising therapeutic target for addressing both the physiological and psychological dimensions of depression. Interventions such as probiotics, prebiotics, dietary modifications and emerging therapies like fecal microbiota transplantation and vagus nerve stimulation offer innovative avenues for treatment. Future research should focus on standardizing methodologies, personalizing interventions based on individual microbiome profiles, and conducting long-term studies to fully explore the therapeutic potential of these approaches.

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Ethical consideration
This review is based exclusively on previously published data, all of which are publicly accessible through academic databases and journal publications. As no new patient data was collected or analyzed, ethical approval was not required.

Conflict of interest statement
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