International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
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ARTICLE TITLE	MICROBIOTA-GUT-BRAIN AXIS IN MAJOR DEPRESSION: PATHOPHYSIOLOGY AND PSYCHOBIOTIC INTERVENTIONS
DOI	https://doi.org/10.31435/ijitss.1(49).2026.4809
RECEIVED	14 January 2026
ACCEPTED	08 March 2026
PUBLISHED	17 March 2026
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MICROBIOTA-GUT-BRAIN AXIS IN MAJOR DEPRESSION: PATHOPHYSIOLOGY AND PSYCHOBIOTIC INTERVENTIONS

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ABSTRACT

Introduction: The microbiota-gut-brain (MGB) axis is a complex network of interactions between the gastrointestinal tract and central nervous system. Increasing numbers of evidence indicates that its dysregulation may be implicated in contributing to the pathophysiology of depression. Changes in gut microbial profile, gut permeability, immune activation and microbial metabolite generation (especially short-chain fatty acids and neurotransmitter precursors) seem to impact neuroinflammatory pathway modulation and neurotransmission, with effect on mood and behavior.
Aim of the Study: To identify the most effective treatments for the regulation, modulation, and management of the MGB axis in depressive disease, and to summarize available evidence for the potential treatment of depression via microbiota-mediated modulation, such as probiotics, prebiotics, dietary modification, and fecal microbiota transplantation.
Materials and Methods: This paper reviews the literature in the PubMed database, and applies the following keywords: "microbiota-gut-brain axis", "gut-brain axis", "psychobiotics", "depression", "gut microbiota", "vagus nerve signaling", "fecal microbiota transplantation".
Conclusions: There are evidences for a central role of the MGB axis in depression along immune, metabolic and neural circuits. According to preclinical and emerging clinical evidence, modulation of gut microbiota (i.e., psychobiotics, prebiotics, high fiber diets, and fermented foods) can restore microbial balance, maintain barrier function, reduce neuroinflammation, and ameliorate neurogenesis, thereby attenuating depressive behaviors. However, heterogeneity in experimental designs, strains, and populations highlights the importance of establishing standardized guidelines and conducting large-scale randomized trials for microbiome-based therapies.

KEYWORDS

Microbiota-Gut-Brain Axis, Psychobiotics, Depression, Gut Microbiota

CITATION

Jan Pietrzak, Dominika Błonka, Aleksandra Jaskulska, Magda Skudzińska, Karolina Wołk, Janina Pohrybieniuk, Filip Kochański, Maria Irena Grys, Magdalena Bartold, Kamil Rajczyk. (2026) Microbiota-Gut-Brain Axis in Major Depression: Pathophysiology and Psychobiotic Interventions. *International Journal of Innovative Technologies in Social Science*. 1(49). doi: 10.31435/ijitss.1(49).2026.4809

Introduction

Depression is a major global health burden with low treatment success and recurrent GI symptoms. More evidence suggests gut microbiota dysbiosis in the pathophysiology of depression. High-throughput sequencing and fecal transplantation [1] evidence in depressed patients that gut microbiota profiles differ, and transferring these microbiota to rodents results in depressive behaviour. Communication across microbiota-brain mediates through neural (vagal), immune (cytokine), and metabolic (microbial metabolites, neurotransmitters, hormones) pathways and impacts neuroinflammation, neuroendocrine function, and neurotransmitter synthesis [3]. In particular, microbial metabolites like short-chain fatty acids can regulate neurogenesis and blood-brain barrier function [15], and gut bacteria may impact tryptophan-serotonin metabolism [16]. These two-way exchanges imply that the gut is a "virtual organ," mediating brain function [1, 17]. Translation studies corroborate therapeutic modulation of the microbiota: the modulation of depressive symptoms in probiotic, prebiotic, and dietary interventions has been some effective [16,18], but the results are variable. This review describes the composition and function of the gut microbiota, the functioning of the microbiota-gut-brain axis, the clinical and preclinical evidence supporting microbiota as associated with depression, and emerging microbiome-based therapies. Synthesizing these new findings, we illustrate how the treatment of depression with gut-brain axis blockade could yield new strategies. In this work we describe an incredibly complex ecosystem of microorganisms known as gut microbiota of our human gastrointestinal tract.

The Human Gut Microbiota

In adults, this microbial ecosystem consists of about 100 trillion microorganisms, including bacteria, archaea, viruses, and fungi community members [1, 6]. Of these, the bacteria are ubiquitous, with Bacteroidetes and Firmicutes phyla prevalent in various populations [8]. Interestingly, the gut microbiota contains a genetic repertoire that is around 150 times the size of the human genome, which represents the gut microbiome's fundamental role in function [10]. Due to its high metabolic potential and impact on host physiology, the gut microbiota can be characterized as a "virtual organ" [9]. The gut microbiota has several key functions contributing to host health. It ferments unreacted food fibers into short chain fatty acids (SCFAs) including acetate, propionate and butyrate as it is an important source of energy for the colonocytes and is an important contributor to modulating host-mediated immune responses [7]. Further, gut microorganisms also play a role in the production of key vitamins like vitamin K and a number of B-group vitamins, and synthesis neurotransmitters, including gamma-aminobutyric acid (GABA) and serotonin precursors, which could modulate gut and brain processes directly [12]. Moreover, the microbiota contributes to maintenance of intestinal barrier quality by influencing tight junction proteins and regulating local immune activation, a process which is necessary for the prevention of systemic inflammation [5]. Metabolic byproducts and structural constituents such as lipopolysaccharides and peptidoglycans are produced by the microbiota that constantly teaches the immune system and promotes gut-associated lymphoid tissue (GALT) formation [3]. The gut microbiota becomes established early in life at birth and stabilizes to become relatively stable adult-like in the first years of life [13]. Nevertheless, its structure remains plastic and influenced by a variety of factors such as dietary adjustments, antibiotic susceptibility, psychological stress, and disease [14]. Dysbiosis, defined as alterations in microbial composition, can decrease microbial diversity and lead to metabolic and immunologic dysfunctions, and potentially impact the host systemically as well as CNS [2]. Strong evidence of an association between gut microbiota and brain functions exists. More than 90% of microbial cells in the body are found in the gastrointestinal tract [11], and the bidirectional communication between the gut and the brain, described as the gut-brain axis, is now seen as central to neurodevelopment and behavior. Studies in germ-free animals, which are devoid of an indigenous microbiota, have demonstrated exaggerated hypothalamic-pituitary-adrenal (HPA) axis responses to stressors and changes in neurotransmitter systems, showing that gut microorganisms are critical to their influence in regulating neuroendocrine systems in addition to inducing emotions [4].

The Microbiota-Gut-Brain Axis: Mechanisms of Communication

Microbiota-gut-brain axis is a complicated, bidirectional system connecting neuronal, immunological, metabolic and endocrine cues in the gastrointestinal tract and the central nervous system. The vagus nerve, through afferent fibers, is one of the major neural pathways through which messages from the gut to the brain, including microbial signals (short-chain fatty acids [SCFAs], tryptophan metabolites and bacterial peptides), are relayed through the gut [19,20]. Such molecules can either stimulate enteroendocrine cells or actually excite vagal afferents, thereby modulating brain circuits that control mood, anxiety and stress. In turn, efferent autonomic signals – transmitted down the sympathetic and parasympathetic pathway – control the motility and secretions of the gut [24]. Poor microbe community, which is represented by lack of diversity of microorganisms, can damage the integrity of the intestinal barrier, increasing permeability-a situation that is called a "leaky gut" [21]. This allows bacterial materials, such as lipopolysaccharides (LPS), to enter systemic circulation and induce inflammatory responses. Peripheral proinflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) may cross the blood-brain barrier or signal through endothelial and glial cells, triggering neuroinflammation [23,26,33]. Most importantly, those inflammatory mediators were found to interact with the pathophysiology of depression, including reports of the high cytokine levels in mood disorders in numerous studies. Gut Microorganisms ferment dietary substrates - including amino acids such as tryptophan - into different bioactive compounds. Indole derivatives regulate the serotonergic and glutamatergic pathways [25]. The SCFAs acetate, propionate and butyrate have been fermented by fiber, and then enter circulation, where they may cross over the blood-brain barrier; this has a key influence on microglial maturation, increases neurotrophic factor expression and supports neurogenesis [27,29]. Furthermore, gut microbes can influence the production and availability of important nutrients such as serotonin, dopamine and GABA. About 90% of the body's serotonin is synthesized in the gut by enterochromaffin cells; it requires microbial metabolites for its activity [39]. Gut microbes direct tryptophan with a low concentration via indoleamine 2,3-dioxygenase (IDO) to the kynurenine pathway and the result of diminished levels of serotonin release becomes an increased attempt to diminish the synthesis of serotonin. Probiotic treatments such as

bifidobacteriaceae treatment for patients with major depressive disorder have been demonstrated to increase tryptophan levels and improve mood symptoms [38]. Some bacteria also generate GABA and dopamine precursors, confirming their ability to exert direct effects on neurotransmission and emotions. Moreover, the endocrine system, especially the hypothalamic-pituitary-adrenal (HPA) axis, acts in both the gut and gut-brain interconnected environment. Germ-free animal models show overreactive hypothalamic-pituitary-adrenal (HPA) axis responses to stress, high corticosterone and this might be ameliorated with probiotic-related colonization [28]. Chronic inflammatory signaling and altered gut-derived afferent inputs may underpin HPA axis activation in dysbiotic media, keeping high cortisol levels, and reinforcing barrier dysfunction and microbiome dysbiosis. Pro-inflammatory cytokines and stress hormones long-term dose exposure diminish the expression of brain-derived neurotrophic factor (BDNF) in hippocampus resulting in reduced neuronal plasticity. SCFAs provide neuroprotection by upregulating BDNF levels and enabling neuronal survival, particularly butyrate [27]. A strong intestinal barrier separates commensal microorganisms from the immune system but dysbiosis, inflammation, or long term stress can also cause the disruption of tight junction proteins, which can lead to a higher permeability of the gut wall and the blood-brain barrier [22]. Restoring barrier integrity of gut - including probiotics supplementation - is related to greater resilience to stress and improved behavioral outcomes in preclinical models [37].

Altered Gut Microbiota in Depression: Clinical and Preclinical Evidence

Increasing evidence from clinical and preclinical research supports the contribution of changes in the gut microbiota for the pathophysiology of depression. Several human studies have reported large-scale compositional adjustments in the gut microbiota in depressed individuals. In general, the low percentage of beneficial genera flora of the gut including Faecalibacterium, Lactobacillus, Bifidobacterium is generally found in depressive states, and the increased genera of microbial potentials including Streptococcus, Klebsiella, Parasutterella, and Phascolarctobacterium are associated with depressive states [32,36]. This variability is most likely due to geographical, dietary, and methodological differences in microbiota research on psychiatric conditions that demonstrate the need of standardized protocols. The frequent co-occurrence of gastrointestinal (GI) disorders and depression further underline the relevance of gut dysbiosis in mood regulation. Functional bowel disorders like irritable bowel syndrome (IBS) are even more common among those affected by depression than in the general population [30]. Patients with high levels of depression may experience a greater burden of GI symptoms, and this correlates to higher rates of mood and anxiety disorders in patients with IBS. Shared disturbances in the microbiota-gut-brain axis may explain this overlap. Indeed, recent studies show that the gut microbiota composition of depressed individuals suffering from IBS is significantly disordered to a greater extent than for individuals without comorbid GI symptoms, indicating an additive or synergistic pathogenesis [34]. But quite astonishingly, fecal microbiota transplantation (FMT) studies have led to some of the strongest causal support for the contribution of gastrointestinal microbes to depression. In leading work of Kelly et al. (2016) and Zheng et al. (2016), fecal microbiota transplantation from depressed human donors to microbiota-depleted rodents induced depression- and anxiety-like behaviors in the recipient animals. These animals showed core depressive phenotypes including anhedonia, decreased locomotor activity and behavioral despair. Furthermore, neurochemical studies showed elevated levels of hippocampal cytokines of interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), as well as metabolic disruption of tryptophan signaling process and kynurenine pathway activation. These results support the suggestion that gut strains of microbiota in depressed hosts are potent enough in inducing central nervous system alterations that mimic the core features of depression [33, 36]. In animal models of depression, the confluence of stress, microbiota, and mood regulation have been improved. Chronic stress paradigms in rodents (e.g., chronic mild stress (CMS) or social defeat stress) induce depressive-like behaviors and gut microbiome effects [35]. Such stress-induced adjustments in the microbial makeup are ameliorated by probiotics or prebiotics, which simultaneously treat depressive behaviour. In contrast, antibiotics depleting the gut microbiota or keeping animals in germ-free environmental conditions can lead to exaggerated stress responses that decrease the level of brain-derived neurotrophic factor (BDNF) and brain neuroplasticity [31]. These findings support the crucial contribution of gut microorganisms in the maintenance of emotional resiliency and stress coping. Of importance, a preclinical model supports the gut microbiota-brain relationship as an intrinsic bidirectional one. Microbial communities not only control brain physiology and personality but also central nervous system (CNS) abnormalities (e.g., repeated administrations of corticosterone or surgical vagotomy) cause fundamental changes in composition of the gut microbiota [31]. This two-way dialogue suggests that stress and depression can result from, and together contribute to, microbial dysbiosis and possibly that this development may help establish a vicious

pattern that underlies mood disturbances. Both clinical findings and preclinical evidence convergent suggests that changes in gut microbiota are highly related to depression. The observed changes may be due to a complex interaction among environmental, genetic, immunological, and microbial processes, which provide potential targets for new therapeutic strategies on the microbiota-gut-brain axis.

Therapeutic Interventions Targeting the Microbiota

New findings are pointing out the gut microbiota as a target of modulation potential novel therapeutic approaches to therapeutic intervention in depression. There are many interventions such as probiotics, prebiotics, dietary changes, and fecal microbiota transplantation, which focus on restoring homeostasis of the microbial community, reducing neuroinflammation, and achieving homeostasis of neurotransmitter balance.

Probiotics (Psychobiotics):

Multiple clinical trials have examined the effects of probiotic supplementation on reducing depressive symptoms. These "psychobiotics" often include strains of the genera Lactobacillus and Bifidobacterium, generally in combination. Some RCTs report positive outcomes. Clostridium butyricum (MiyaIRI 588), for example, as an adjunctive medication, increased the response rate among patients with major depressive disorder (MDD) compared to the placebo group by 70% [18]. In another eight-week study that utilised a Lactobacillus helveticus and Bifidobacterium longum combination, scores on the Beck Depression Inventory (BDI) were significantly lower than those of placebo [43]. In a second trial with 40 subjects suffering from MDD, supplementation with L. acidophilus, B. bifidum and L. casei were able to improve BDI and also have a lowering of markers of systemic inflammation, notably C-reactive protein (CRP) and insulin [34,40], indicating a synergistic impact on mood, metabolism and inflammation. But not all the cases are equally good. For example, a larger study with 79 adults using the same combination L. helveticus/B. longum probiotic blend also reported no significant difference compared with placebo [44]. Meta-analyses have recognized considerable heterogeneity in the study design across studies such as probiotic strains, dosages, trial durations, and patient characteristics. Notwithstanding these discrepancies, the systematic literature provides evidence that psychobiotics serve as a viable adjunctive intervention with the potential to modify neurotransmitter metabolism and decrease neuroinflammation and stress [34,44].

Prebiotics and Synbiotics:

Prebiotics, chiefly dietary fibers and non-digestible oligosaccharides, preferentially stimulate the growth of good gut bacteria. Even on a small scale, some studies indicate that prebiotic, including galactooligosaccharides (GOS) have low-moderate mood and anxiety improving effects may be enhanced by enhanced SCFAs synthesis and BDNF upregulation [45]. Another approach under active investigation are the synbiotics (which consist of prebiotics and probiotics combined). Early findings indicate a good tolerability and mood benefit, but solid clinical evidence for depressive disorders is lacking. Bigger, standardized trials are needed to prove efficacy.

Dietary Interventions:

Diet is a powerful regulator of the gut microbiota and therefore a key factor for mental health treatments. A Mediterranean-based dietary approach—high in fiber and fruits, vegetables, whole grains, legumes, fish, and unsaturated fats—is associated with reduced risk of depression [42]. In clinical trials, a Mediterranean-like diet may decrease depressive symptoms, and this has been mediated, possibly, through increased microbial diversity in the gut and increased production of SCFA [41]. In contrast, Western diets high in refined sugars, saturated fats, and processed foods favor dysbiosis and systemic inflammation. The modern academic discipline of nutritional psychiatry encourages diet-based dietary habits that promote microbial homeostasis as a preventive and therapeutic technique for mood disorders, and this is an evolving field of research.

Fecal microbiota transplantation (FMT):

FMT provides a potent vehicle for repopulating gut microbiota communities. Though it is currently predominantly established in the gastrointestinal field for a variety of conditions like Clostridioides difficile infection, initial investigations also suggest it may be useful as a treatment modality in psychiatry. Examining case reports and early-phase trials using FMT from healthy donors toward treatment-resistant patients with depression. Proximity to healthy donor microbiota has been shown in animal models to relieve stress-related behaviors [36]. The use of FMT in the treatment of depression so far is experimental and in need of adequate clinical trials to ensure its safety, efficacy, and long-term effects.

Other Emerging Therapies:

Appropriate SCFAs for their neuroprotective and anti-inflammatory effects (e.g., sodium butyrate) are being investigated. Another evidence is that fermented foods (kefir, kimchi, etc.) reduce depression scores especially in stress patients as a potential source of microbial composition and inflammatory markers [46]. Broad-spectrum antimicrobials, in contrast, may have a short-term anti-inflammatory effect but frequently have pro-inflammatory/antimicrobial effects on the microbiota, and long-term association with prolonged antibiotic use can be established where increased depression is at risk. Thus, future therapies attempt to encourage a durable and homeostasis in the gut ecosystem rather than to perturb microbial communities broadly and generally. In short, target therapeutics in the gut microbiome are an important frontier in the treatment of depression. Although probiotics, prebiotics, dietary manipulation, and possibly FMT can prove valuable, they have the potential benefit of the large-scale clinical benefits, standardizing protocols and conducting trials on a worldwide scale are also required to capitalize on the significant clinical benefits of microbiota-targeted therapies.

Challenges and Future Directions

While the gut-brain axis represents a promising frontier for understanding and treating depression, significant challenges still remain. Advances are expected to be made overcoming methodological variation, improving mechanistic insight, improvement in trial design, improvement in clinical trial design, or translation of fundamental research into practice. Heterogeneity and Mechanistic gaps:

Currently published investigations of microbiota changes in depression and microbiota-based depression are very heterogeneous in methods - differences in sequencing depth, sample sizes, diagnostic thresholds, conditions, and individual demographics contribute to poor reproducibility in our results concerning some microbiome signatures. Sufficient standards for the collection and sequencing and analysis of samples are clearly required for reproducibility and meta-analysis synthesis. In addition, most other studies thus far have been descriptive in nature concentrating on taxonomic changes, and not functional alterations. Multi-omics approaches through metagenomics, microbiome analysis, metabolomics, transcriptomics, proteomics are important to elucidate stable functional markers associated with depressive pathology (e.g., microbial gene pathways, metabolite profiles). Crucially, the exact pathophysiological pathways underlying gut dysbiosis and depression neural (vagal afferents), immune (cytokine signaling), metabolic (neurotransmitter precursor modulation) pathways need to be defined in humans as yet. Moreover, although gut-to-brain (afferent) signaling has been well-studied, much less is known about the reverse (efferent) pathways: how central states, including chronic stress, psychiatric medications or mood episodes, alter the gut microbiota. A bidirectional model of the gut-brain interaction is required to fully elucidate the etiology of depression.

Clinical Trial Design:

Previous probiotics and prebiotics trial methods feature small sample sizes, limited duration of treatment and mechanistic endpoints. It is proposed to design future RCTs with larger and stratified cohorts in a population and a meticulous characterization of the baseline microbiota, inflammatory state and psychiatric history. In addition, trials should explore high-throughput, reliable strains of microorganisms as well as use objective biomarkers such as fecal microbiome sequencing, blood cytokine levels, SCFA quantification, neuroimaging and validated clinical outcomes measures. It is also possible to determine responders by identifying specific subgroups (for example, patients with elevated inflammatory levels, gastrointestinal comorbidities, such as IBS, or particular dysbiotic profiles) to design targeted psychobiotic medicine to individuals who respond. Integrating the psychobiotic with standard antidepressant therapies is a promising approach since initial data appear to indicate that probiotics may augment antidepressant efficacy and alleviate associated symptoms, such as GI complaints or weight gain.

Translational Problems:

As valuable as animal models like chronic stress-induced dysbiosis, with which scientists deal, with respect to human psychiatric diseases there are still areas of applicability that might benefit greatly. These differences include the composition of gut microbiota, brain development, and immune responses across species. This translational gap calls for new tools such as humanized microbiota models, organ-on-a-chip technologies replicating the gut-brain axis, and computational models which can model the interactions between microbiome and CNS. A key therapeutic question for humans to be addressed is whether targeting particular microbial metabolites (e.g., by supplementing with butyrate) will generate the same therapeutic results as doing broader ecological interventions (e.g., altering diets or using microbiota therapies). And it will

be addressing this question which will decide if in the future therapies should focus on precise molecular targets, or how they are better directed toward targeting wider ecosystem dynamics.

Emerging Therapies:

Newer methods could broaden therapeutic options. Approaches for microbiome engineering, such as designer probiotics with improved functions and bacteriophage therapy for pathogenic bacteria, may allow focused interventions. Furthermore, "postbiotics" that release purified microbial metabolites (i.e., SCFAs, neurotransmitter precursors) without the presence of live bacteria are currently being studied as safer, more controllable treatments. Additionally, understanding the importance of early-life microbiome emergence enables prevention efforts. Studies of maternal diet, infant feeding, and antibiotic use in the early childhood period might reveal factors that are modifiable and impact long-term mental health trajectories. Finally, by combining microbiome data with host genomics, environmental exposures (e.g., stress, diet), and psychosocial factors, we will contribute to a systems biology approach to the understanding of depression, and enable personalized and predictive mental health care.

Disclosure

Conceptualization: Jan Pietrzak and Aleksandra Jaskulska; Methodology: Janina Pohrybieniuk; Software: Filip Kochański; Check: Maria Grys and Janina Pohrybieniuk; Formal analysis: Kamil Rajczyk and Magdalena Bartold; Investigation: Maria Grys and Karolina Wołk; Resources: Filip Kochański; Data curation: Kamil Rajczyk; Writing - rough preparation: Aleksandra Jaskulska and Jan Pietrzak; Writing - review and editing: Magdalena Bartold and Dominika Błonka; Visualization: Magdalena Skudzińska; Supervision: Aleksandra Jaskulska; Project administration: Karolina Wołk and Dominika Błonka; Receiving funding - no specific funding. All authors have read and agreed with the published version of the manuscript.

Financing statement: This research received no external funding.

Conflict of interest: The authors deny any conflict of interest.

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgement in the analytical process.

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