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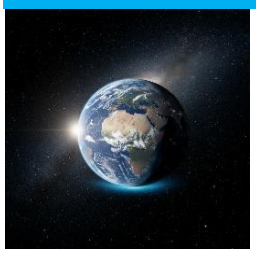

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The role of gut microbiota in major depressive disorder: understanding the microbiota-gut-brain axis

Julia Lorek, ORCID https://orcid.org/0009-0000-4738-074X
E-mail julka.lorek9@gmail.com
University Clinical Hospital in Wroclaw, Borowska 213, 50-556 Wrocław, Poland

Magda Sawin, ORCID https://orcid.org/0009-0003-7893-804X
E-mail m.sawin29@gmail.com
University Clinical Hospital in Wroclaw, Borowska 213, 50-556 Wrocław, Poland

Wiktoria Brzozowska, ORCID https://orcid.org/0009-0005-3615-8023
E-mail g.wiki123@gmail.com
University Clinical Hospital in Wroclaw, Borowska 213, 50-556 Wrocław, Poland

Daniel Grobecki, ORCID https://orcid.org/0009-0005-1724-7784
E-mail danielgrobecki00@gmail.com
University Clinical Hospital in Wroclaw, Borowska 213, 50-556 Wrocław, Poland

Franciszek Jabłoński, ORCID https://orcid.org/0009-0006-3715-1429
E-mail franciszek.henryk.jablonski@wp.pl f.jabłoński@umw.edu.pl
University Clinical Hospital in Wroclaw, Borowska 213, 50-556 Wrocław, Poland
Wroclaw Medical University, Physiology and Pathophysiology Department, Chałubińskiego 10, 50-556, Wroclaw, Poland

Hanna Jabłońska,ORCID:https://orcid.org/0009-0001-0849-7352
E-mail haniatelega1704@gmail.com
University Clinical Hospital in Wroclaw, Borowska 213, 50-556 Wrocław, Poland
Silesian Higher Medical School in Katowice, Adama Mickiewicza 29, 40-085, Katowice, Poland

Adam Jarczak, ORCID: https://orcid.org/0009-0008-0801-0058
E-mail: adamjarczak98@gmail.com
University Clinical Hospital in Wroclaw, Borowska 213, 50-556 Wrocław, Poland

Jakub Korybski, ORCID https://orcid.org/0009-0006-4499-3149
E-mail jakub.korybski@gmail.com
University Clinical Hospital in Wroclaw, Borowska 213, 50-556 Wrocław, Poland

Katarzyna Szeliga, ORCID https://orcid.org/0009-0005-3006-2178
E-mail lek.kszeliga@gmail.com
University Clinical Hospital in Wroclaw, Borowska 213, 50-556 Wrocław, Poland
Silesian Higher Medical School in Katowice, Adama Mickiewicza 29, 40-085, Katowice, Poland

Patrycja Waszkiewicz, ORCID https://orcid.org/0009-0000-2403-705X
E-mail Patrycja.waszkiewicz.md@gmail.com
University Clinical Hospital in Wroclaw, Borowska 213, 50-556 Wrocław, Poland
Silesian Higher Medical School in Katowice, Adama Mickiewicza 29, 40-085, Katowice, Poland

Corresponding Author: Julia Lorek, E-mail: julka.lorek9@gmail.com

Abstract

Background: Depression is a common and complex psychiatric disorder that poses a significant burden on individuals and healthcare systems. Despite extensive research, its pathogenesis remains incompletely understood, and many patients do not respond adequately to standard treatments. The gut and brain communicate through a bidirectional pathway known as the gut-brain axis. Increasing attention has been given to the role of gut microbiota in regulating this communication, leading to the concept of the microbiota-gut-brain axis (MGBA).
Aim: This review aims to synthesize current evidence on the role of gut microbiota in major depressive disorder, with emphasis on MGBA-related pathways.
Materials and Methods: A literature review was conducted using PubMed and Scopus. Relevant studies addressing the relationship between gut microbiota and depression were selected.
Results and Discussion: The gut microbiota influences central nervous system through several interconnected pathways, including neuronal signaling, immune modulation, regulation of the hypothalamic-pituitary-adrenal (HPA) axis, and production of bioactive metabolites. Dysbiosis

may lead to increased intestinal permeability, inflammation, HPA axis dysregulation, and disturbances in neurotransmission, all of which have been associated with depressive symptoms. **Conclusions**: Changes within the MGBA may play a role in the pathophysiology of depression. Gut microbiota represents a promising target for future therapeutic strategies. However, further research is needed to clarify causal relationships and develop effective interventions.

Key words: gut microbiota, microbiota-gut-brain-axis, gut dysbiosis, gut-brain axis, major depressive disorder, depression

1. Introduction

Major Depressive Disorder (MDD) is the most common psychiatric disorder, affecting approximately one in five individuals over their lifetime(1,2). According to the World Health Organization (WHO), depression currently affects an estimated 350 million people globally and is projected to become the leading cause of (disability) disease burden by 2030(3,4). It is a chronic and complex disease, characterized by symptoms such as persistent low mood, loss of interest or pleasure, appetite and weight changes, sleep disturbances, psychomotor changes, fatigue, cognitive difficulties, feelings of guilt or worthlessness, suicidal thoughts(2,5).The pathogenesis of major depressive disorder(MDD) is regarded as multifactorial, resulting from interactions among biological, genetic, environmental and psychosocial factors. Traditionally, depression was associated with abnormalities in monoaminergic neurotransmission, particularly involving serotonin, norepinephrine, and dopamine. However, emerging evidence suggests a far more complex ethiology.(6). Several hypotheses are currently regarded as particularly influential in explaining the underlying mechanisms of MDD. The HPA axis dysfunction hypothesis highlights that stress-induced abnormalities of the HPA axis, resulting in elevated cortisol levels, are associated with depression(7). The neuroinflammatory hypothesis implicates excessive production of proinflammatory cytokines which lead to development of depressive symptoms by affecting brain tissue, modulating the monoaminergic system, and triggering neurotoxic processes(7,8). The genetic and epigenetic vulnerability hypothesis identifies some genes that increase susceptibility to depression, while the brain remodeling hypothesis emphasizes structural and functional changes in the prefrontal cortex, hippocampus, and amygdala, including hyperactivity in the amygdala, striated nucleus, limbic and subcortical regions and reduced glial cell density(3,9). Finally, the social-psychological hypothesis points to traumatic or stressful life events as major risk factors for depression(1,3,10). Despite extensive research, a single, clearly defined mechanism responsible for the pathogenesis of depression has not yet been fully elucidated (11).

Recently, the gut microbiota has been increasingly considered as an important component in the pathogenesis of depression(7,12,13).

The human gastrointestinal tract is colonized by a diverse community of microorganisms that participate in maintaining gastrointestinal homeostasis. Beyond their local functions, the gut microbiota and products of its metabolism can affect distant organs, including the central nervous system(14). This communication pathway between the gut microbiota and brain is known as the microbiota-gut-brain axis, which operates through metabolic, neuronal, immunological, and neuroendocrine pathways. Through these interconnected pathways, the gut microbiota can influence mood, behavior, and neuronal signaling. Clinical studies have demonstrated that patients with depressive disorders exhibit distinct changes in gut microbial profiles compared to healthy controls, suggesting a potential association between microbial imbalance and depressive symptomatology(7,15,16).

In this review, we provide a critical overview of the current understanding of the relationship between gut microbiota and major depressive disorder. We discuss the composition and functional role of the gut microbiota, highlighting its protective, metabolic and immunological functions that contribute to host homeostasis. Particular attention is given to the pathways of communication within microbiota-gut-brain-axis, including neural, metabolic, neuroendocrine and immune signaling. Further, we address the mechanisms linking gut dysbiosis to depression, with a focus on its impact across these inerconnected pathways within the microbiota-gut-brain-axis.

2. The Role of Gut Microbiota in host homeostasis

The gut microbiota is defined as the community of microorganisms that colonize the gastrointestinal tract, including bacteria, archaea, viruses, and fungi, together with their collective genetic material and metabolic products(17). The gastrointestinal tract harbors the largest and most densely populated microbial community in the human body, with estimates indicating that it contains up to 10^{14} microbial cells, exceeding the total number of human cells in the body. It is estimated that the gut microbiota comprises more than 1000 bacterial species(18). In healthy individuals, the gut microbiota is dominated by several major bacterial phyla, including *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria*, with *Firmicutes* and *Bacteroidetes* together accounting for approximately 90% of the total microbial composition(17,19,20). The composition and diversity of the gut microbiota vary between

individuals and across different regions of the gastrointestinal tract. As one moves along the digestive tract from the esophagus to the rectum, substantial differences can be observed in both the diversity and abundance of microorganisms. The number of bacteria increases progressively from approximately 10^1 cells per gram of content in the esophagus and stomach to around 10^{12} cells per gram in the colon and distal intestine(21,22).

The structure of the gut microbiota is shaped by interplay between host-related factors like age, genetics, immune function, and physiological conditions, as well as environmental influences such as diet, lifestyle, stress, and exposure to environmental chemicals. The composition of the gut microbiota is relatively stable, however Western diet, antibiotics over-use, environmental pollutants may lead to persistent alterations in microbial community, leading to variety of diseases(20). These changes have been linked not only to gastrointestinal disorders, such as inflammatory bowel disease(IBD) and irritable bowel syndrome (IBS), but also to metabolic conditions, including diabetes, obesity and various types of cancer. Furthermore, gut dysbiosis has been associated with neurological and mood disorders, like Alzheimer's disease (AD), autism spectrum disorder (ASD), depression and anxiety(23).

Intestinal microorganisms plays a fundamental role in maintaining gastrointestinal and systemic homeostasis through a range of interrelated functions. These include structural support of the intestinal barrier, protection against pathogens, metabolic activity involving nutrient processing and production of bioactive metabolites, as well as regulation of immune responses(21). Through these coordinated mechanisms, gut microbiota may also influence host physiology beyond the gastrointestinal tract, through modulation of metabolic, immune and nervous system functions(14).

2.1 Structural and protective function

The gut microbiota maintains the structural integrity of the intestinal barrier, thereby protecting the host by limiting the invasion and colonization of pathogenic microorganisms(24). This function is closely related to the organization of the intestinal epithelium, which consists of a single layer of epithelial cells connected by intercellular junctional complexes, including tight junctions, adherents junctions and desmosomes, that regulate paracellular permeability(25). The gut microbiota contributes to the regulation of epithelial tight junctions and intestinal permeability, thereby supporting the stability of the intestinal environment. Disturbances in microbial composition may disrupt barrier integrity, resulting in increased intestinal permeability, inflammation, and the development of various diseases(26). Moreover, intestinal

commensals promotes colonization resistance by competing with other microorganisms for limited nutrients and ecological niches within the gut and by directly inhibiting competing bacteria, through the production of bacteriocins and bacteriophages. The mucus layer of the colon, whose main structural component is the glycoprotein MUC2, represents an important element of epithelial defense by limiting bacterial penetration and supporting intestinal barrier function(27).

2.2 Immunomodulation

The close interaction between intestinal microorganisms and the host plays a fundamental role in shaping both local and systemic immune responces(28). The intestinal epithelium forms an important interface where microbial signals are continuously sensed by immune cells, including antigen-presenting dendritic cells. This allows for ongoing communication between the microbiota and the host(29). Through these interactions, commensal bacteria influence the differentiation of naive CD4+ T cells into major subsets such as Th1, Th2, Th17 and regulatory T (Treg) cells, thereby contributing to the balance between pro- and anti-inflammatory responses(21,30). Moreover, the presence of these commensal microbes is necessary for the proper maturation of gut-associated lymphoid tissue (GALT), highlighting its role in immune system development(24). In addition to shaping immune cell differentiation, the gut microbiota contributes to mucosal defense mechanisms. It has been shown to stimulate the production of antimicrobial peptides (AMPs), including cathelicidins, defensins and C-type lectins, and to promote the secretion of immunoglobulin A (IgA), which helps to limit microbial translocation and maintain intestinal homeostasis(21). Metabolites produced by the gut microbiota, particularly SCFAs, influence immune system by modulating epithelial barrier and mucosal immune cells. These effects are mediated through interactions with G protein-coupled receptors (GPCRs), such as GPR41, GPR43 and GPR109A and activation of peroxisome proliferator-activated receptor gamma (PPARγ), which together influence both innate and adaptive immunity(31). Furthermore, the influence of gut microbiota extends beyond the intestinal environment. Structural components of bacteria, such as lipopolysaccharide (LPS), flagella and peptidoglycan, interact with host receptors and contribute to the modulation of systemic immune responces(32).

2.3 The role of microbial metabolites

One of the main ways in which the gut microbiota affects host physiology is through the production of metabolites(33). Metabolites produced by the gut microbiota during the

fermentation of dietary fiber and other indigestible carbohydrates are mainly short-chain fatty acids (SCFAs), which represent one of the most important products of microbial metabolism in the gut(34). Among the short-chain fatty acids, acetate, propionate, and butyrate are the most predominant. They are usually found in the gut in approximate molar proportions ranging from 3:1:1 to 10:2:1(35). These metabolites play an important role in maintaining intestinal homeostasis by supporting epithelial cell function, strengthening intestinal barrier integrity, and modulating immune responses(36). In particular, butyrate plays a vital role in maintaining intestinal barrier integrity by enhancing tight junctions assembly and promoting mucin production, thereby limiting bacterial translocation. Through these effects, SCFAs contribute not only to local GI homeostasis, but also to the prevention of systemic inflammation, highlighting their anti-inflammatory effects. These effects are mediated through SCFA interactions with G protein- coupled receptors (GPCRs) and inhibition of histone deacetylases (HDACs), thereby influencing gene expression and cellular signaling pathways(37,38). The gut microbiota plays a significant role in tryptophan metabolism. Tryptophan is metabolized through three main pathways: the serotonin and kynurenine pathways in host cells, and the indole pathway mediated by the gut microbiota. Within this microbial route, tryptophan is converted into a range of indole derivatives, such as indole-3-acetic acid, indole-3-propionic acid, and indole-3-aldehyde. These compounds contribute to intestinal and systemic homeostasis by regulating epithelial barrier function, modulating immune responses, and influencing host signaling pathways, particularly through activation of the aryl hydrocarbon receptor (AhR)(38). Together with SCFAs, microbiota-derived tryptophan metabolites represent important mediators linking microbial activity to host metabolic and immune regulation.

In addition, certain gut bacteria also participates in the synthesis of vitamins, particularly vitamin K and several B-group vitamins, including biotin, cobalamin, folate, riboflavin, thiamine, pyridoxine, pantothenic acid, and nicotinic acid(21,35). Moreover, gut microbiota convert primary bile acids into secondary bile acids, thereby influencing lipid metabolism. Dysregulation in these microbial pathways has been linked to metabolic disorders, including obesity and type 2 diabetes(37).

Importantly, gut microorganisms are capable of producing a range of neuroactive compounds, including neurotransmitters such as serotonin, dopamine and melatonin, as well as gamma-aminobutyric acid (GABA), polyamines and histamine. These microbiota-derived molecules may participate in bidirectional communication between the gut and the nervous system and

can also interact with immune cells, linking metabolic activity of the microbiota with neuroregulatory and immunological processes(39,40).

Taken together, these findings highlight the broad impact of gut microbiota on host physiology and suggest that disturbances in microbial composition may influence systemic processes, including those regulating brain function and mood regulation(41). In this context, the microbiota-gut-brain axis has been proposed to describe the complex interactions between the gut and central nervous system.

3. Microbiota- gut-brain axis

The gastrointestinal tract and the brain are closely connected through a bidirectional communication network known as the gut-brain axis. This system links the enteric nervous system with the central nervous system and enables continuous signaling between the gut and the brain(42). A growing body of evidence suggests that gut microbiota play a role in modulating this communication. Evidence from germ-free (GF) animal models provides strong support for the role of gut microbiota in brain development and function. The absence of microbiota has been associated with structural and functional alterations in the brain, including reduced myelination, changes in hippocampal volume, and changes in anxiety-like behavior. These animals also show an altered stress response, immature microglial phenotype and impaired responses to microbial signals, such as LPS, which may contribute to neuroinflammation. Increased permeability of the blood-brain barrier also has been observed in GF models, suggesting that microbiota play a role in maintaining its integrity(29). Consequently, the concept of the microbiota-gut-brain axis has been proposed to describe the interactions between intestinal microbiota, the gastrointestinal tract, and the central nervous system. Alterations in gut microbiota composition have been associated with changes in emotional regulation, stress responses, and cognitive function, highlighting the importance of this axis in both physiological homeostasis and mental health(43). Communication within the microbiota-gut-brain axis involves several interconnected pathways, including the autonomic nervous system, enteric nervous system, hypothalamic-pituitary-adrenal (HPA) axis, immune system and microbial metabolites(44).

3.1 Neuronal pathway

Neural signaling is a fast responding component of microbiota- gut–brain axis, primarily involving the enteric nervous system (ENS) and the vagus nerve. The ENS, often described as the “second brain”, regulates gut motility, secretion, and local homeostasis, while interacting bidirectionally with the central nervous system and influencing microbial activity and intestinal barrier function(45). The vagus nerve, a main component of the parasympathetic autonomic nervous system, is regarded as the primary neural pathway connecting the gut and the brain. It detects various stimuli, including microbial metabolites, and transmits this information to the central nervous system. Communication between the gut and the vagus nerve may occur either through direct interactions with microorganisms or indirectly through signaling from enteroendocrine cells. These cells release hormones such as cholecystokinin, serotonin, and peptide YY that activate vagal afferent neurons(46,47). Approximately 80% of vagal fibers are afferent, transmitting sensory information from the gut to the brain, while the remaining 20% are efferent fibers responsible for sending regulatory signals from the brain to the gastrointestinal tract. Through these bidirectional pathways, the vagus nerve also participates in the modulation of the hypothalamic-pituitary-adrenal (HPA) axis, which is essential for coordinating the body’s response to stress(48). The vagus nerve is also involved in immune signaling, as it can detect pro-inflammatory cytokines mediated by Toll-like receptors (TLRs) and transmit this information to the brain via afferent pathways. At the same time, efferent vagal signaling can suppress the release of pro-inflammatory cytokines, forming part of the so-called inflammatory reflex(45). In animal studies, mice that underwent vagus nerve transection did not exhibit the typical microbiota-related neurochemical and behavioral changes, highlighting the essential role of vagal signaling in gut-brain communication(49).

Neurotransmitters play an important role in communication within the gut-brain axis. Increasing evidence indicates that gut microbiota can influence brain function and emotional behavior by modulating several neurotransmitter systems, including serotonergic, dopaminergic, noradrenergic, glutamatergic, and GABAergic pathways.This occurs because certain microorganisms can produce neurotransmitters or their precursors, thereby affecting their synthesis and metabolism (50). Among the neurotransmitters involved in gut-brain communication, serotonin (5-HT) plays a particularly important role. Serotonin (5-HT) is a key neurotransmitter involved in the regulation of appetite, gastrointestinal motility, mood, cognition, and sleep. More than 90% of the body’s serotonin is produced in the gastrointestinal

tract by enterochromaffin cells through a process regulated by tryptophan hydroxylase enzymes (TPH1 and TPH2)(51). Moreover, several microbial species can directly synthesized neurotransmitters. *Candida, Escherichia, Enterococcus* and *Streptococcus* have been associated with serotonin production, whereas *Bifidobacterium* and *Lactobacillus are known to* synthesize GABA. In addition, *Bacillus* and *Serratia* are linked with dopamine production, while *Escherichia* and *Saccharomyces* can generate norepinephrine(52). These microbiota-derived neurotransmitters can pass through the intestinal barrier and enter the bloodstream, where they may influence brain function or interact with neural pathways, such as the vagus nerve. Additionally, microbial metabolites can affect enteroendocrine cells and, in this way, influence the production and release of neurotransmitters, contributing to communication along the gut–brain axis(53).

3.2 HPA Axis

The hypothalamic-pituitary-adrenal (HPA) axis represents an important neuroendocrine pathway involved in microbiota- gut-brain axis communication and plays a central role in the physiological response to stress. Activation of the HPA axis begins with the release of corticotropin-releasing hormone (CRH) from the hypothalamus, which stimulates the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. ACTH subsequently acts on the adrenal cortex, leading to the release of glucocorticoids such as cortisol. Under physiological conditions, glucocorticoids exert a negative feedback effect on the HPA axis by inhibiting further CRH and ACTH release, therby maintaining homeostasis(54,55).

As a result of HPA axis activation, cortisol influences brain function by acting on glucocorticoid receptors located in regions such as the amygdala, prefrontal cortex, and hippocampus, which are involved in emotional regulation, executive processes, and memory. The impact of cortisol varies depending on exposure duration, with acute and chronic effects differing in their influence on the brain(56).

The HPA axis also affects the gastrointestinal tract, thereby linking neuroendocrine responses with gut physiology(57). Cortisol acts on various cell types in the gut, including epithelial, immune and enteroendocrine cells, therefore directly influence intestinal function. Through these effects, activation of the HPA axis may alter gut transit time, intestinal permeability, and nutrient availability, ultimately shaping composition of gut microbiota. For instance, exposure to stress in early-life, such as maternal separation, can lead to sustained activation of the HPA

axis, thereby results in negative changes in gut microbiota composition as well as dysregulation of stress responce(58).

In turn, evidence also indicates that gut microbiota can influence HPA axis activity, as alterations in microbial composition have been associated with changes in stress responses and glucocorticoid levels(59). Experimental findings support this bidirectional connection, demonstrating that stress leads to alterations in gut microbiota composition, including a reduction in beneficial bacteria such as *Lactobacillus*. Furthermore, different studies have shown that probiotic supplementation with *Lactobacillus* and *Bifidobacterium* strains restored stress-induced dysregulation of HPA axis. These changes were accompanied with improved cognitive functions and reduced depression- and anxiety- like behaviors, highlighting the interconnection between the HPA axis, gut microbiota and the brain (60).

Taken together, these findings highlight the bidirectional relationship between the HPA axis and gut microbiota, suggesting that their dysregulation may play a role in the development of stress-related disorders, including depression.

3.3 Immune System

The immune system represents another major component of communication within the microbiota-gut-brain axis. It is estimated that approximately 70-80% of the body's immune cells are located in mesenteric lymph nodes(61). Interaction between the gut microbiota and immune system is essential for maintaining intestinal homeostasis. This relationship is primarily regulated by adaptive immune mechanisms, including T cell-mediated control of microbial composition and IgA-dependent maintenance of mucosal balance. Through these processes, the immune system exerts selective pressure on the microbiota, contributing to its stability and proper functioning(32).

However, immune signaling within this axis is not limited to local intestinal responses, but also involves long-distance communication with the central nervous system. Both innate and adaptive immune mechanisms contribute to this bidirectional interaction. The innate immune component includes peripheral cells such as monocytes and macrophages, as well as central nervous system-resident cells like microglia and astrocytes, alongside dendritic cells and innate lymphoid cells in the gut(45). Gut microbiota can modulate immune signaling through pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), located on these intestinal cells. This activation stimulates the release of pro-inflammatory cytokines, including TNF-α, IL-1, and IL-6, which may cross the blood-brain barrier (BBB) and influence brain function by

modulating neurotransmitter systems such as GABA, serotonin, and dopamine(19). A well-known example of such microbial components is lipopolysaccharide (LPS), a structural component of Gram-negative bacterial cell walls. LPS can activate Toll-like receptor 4 (TLR4) expressed on microglia and astrocytes, triggering the production of pro-inflammatory cytokines and promoting neuroinflammatory processes that may influence central nervous system function(62).

Furthermore, the crosstalk between gut microbiota and the immune system plays a vital role in preserving blood-brain barrier (BBB) integrity. Disruption of this barrier, often driven by gut-derived immune activation, can facilitate the translocation of peripheral immune mediators and microbial products into the central nervous system, promoting neuroinflammatory processes(22).

3.4 Microbial metabolites

Gut microbiota produce numerous bioactive metabolites that participate in communication within the microbiota-gut-brain axis. These compounds may act locally in the gastrointestinal tract or enter the bloodstream, cross the blood–brain barrier (BBB), or signal through other pathways to influence brain function and host behavior(63,64).

Short-chain fatty acids (SCFAs) play an important role in gut–brain communication and represent one of the most extensively studied microbial metabolites. They can modulate gastrointestinal and enteric nervous system (ENS) activity, increase the expression of tryptophan hydroxylase 1 (Tph1), a key enzyme in serotonin synthesis in enterochromaffin cells, regulate the production of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), and contribute to anti-inflammatory processes and the maintenance of blood–brain barrier (BBB) integrity(65,66).

Gut microbiota participate in tryptophan metabolism, producing several bioactive compounds, including indole, tryptamine, indole-3-acetic acid (IAA), and indole-3-propionic acid (IPA). Indole, the major bacterial metabolite of tryptophan, can influence intestinal barrier integrity, immune responses, but also brain function and behavior. IPA has been associated with anti-inflammatory effects. Moreover, by directing tryptophan metabolism toward the kynurenine pathway rather than 5-HT pathway, gut microbiota can reduce serotonin availability, thereby contributing to neuropsychiatric disorders, including depression(67).

Bile acids, synthesized in the liver, also interact with gut microbiota and contribute to communication within the microbiota-gut-brain axis. Activation of the intestinal farnesoid X receptor (FXR) induces the production of fibroblast growth factor 19 (FGF19), which can enter the circulation and cross the blood–brain barrier. In animal studies, particularly in mice, this signaling has been shown to suppress HPA axis activity and exert antidepressant-like effects (68).

Additionally, trimethylamine-N-oxide (TMAO), a metabolite derived from microbial choline metabolism, can enter the systemic circulation and cross the blood–brain barrier, where it may contribute to brain pathology and the development of neuropsychiatric disorders(69).

To sum above, the microbiota-gut-brain axis operates through interconnected neuronal, immune, endocrine, and metabolic pathways, that collectively regulate brain function and behavior. Dysregulation of these mechanisms, particularly in the context of gut dysbiosis, may contribute to the pathophysiology of neuropsychiatric disorders, including depression.

4. Gut dysbiosis and Depression

Gut dysbiosis refers to an imbalance in the gut microbiota, characterized by reduced microbial diversity, a loss of beneficial or an increase in potentially harmful bacteria(70). Such disturbances in the composition and abundance of gut microbiota have been associated not only with gastrointestinal diseases but also with neurological and mental disorders(71). Dysbiosis may contribute to the development or exacerbation of depressive symptoms by modulating microbial metabolite production, immune responses, blood-brain-barrier (BBB)integrity, neurotransmitter levels, and the HPA axis(72). For example, in a mouse model of depression, alterations in gut microbiota were accompanied by reduced levels of short-chain fatty acids (SCFAs) and decreased concentrations of neurotransmitters such as norepinephrine and serotonin in the hypothalamus, suggesting a link between dysbiosis and changes in brain neurochemistry(73).

Studies using fecal microbiota transplantation (FMT) provide strong evidence that gut microbiota may play a role in pathogenesis of depression(74). Kelly et al (75), demonstrated that transplantation of gut microbiota from patients with depression into microbiota-depleted rats induced depression-like behaviors. Similar findings were reported by Zheng et al.(76), who showed that transfer of microbiota from patients with depression to germ-

free mice also resulted in depression-like behaviors. These results suggest that gut microbiota may play a role in the development of depression.

4.1 Alterations in gut microbiota composition in depression

Research has shown that individuals with major depressive disorder (MDD) exhibit differences in gut microbial composition compared to healthy individuals. These alterations include changes in microbial diversity and in the relative abundance of certain bacterial taxa. In particular, a decreased abundance of anti-inflammatory bacteria and an increased presence of pro-inflammatory bacterial taxa have been observed(69). Jiang et al. found that patients with major depressive disorder exhibit higher levels of *Bacteroidetes* and *Proteobacteria*, while the abundance of *Firmicutes* was lower. The study also reported increased levels of *Alistipes*, a bacterial genus involved in tryptophan metabolism, which may affect tryptophan availability and consequently influence serotonin production in the gut (77). Consistent with these findings, an increased *Bacteroidetes/Firmicutes* ratio has been reported in patients with MDD, with higher levels of *Bacteroides* and reduced abundance of *Blautia*, *Faecalibacterium*, and *Coprococcus*(69). *Faecalibacterium*, and *Coprococcus* are important producers of short-chain fatty acids (SCFAs), espetially butyrate, which has anti-inflammatory properties, helps maintain the integrity of the intestinal barrier, and reduces gut permeability(78). However, the reported alterations in gut microbiota composition remain inconsistent across studies. For instance, some studies have demonstrated an increased abundance of Bacteroidetes and decreased levels of Firmicutes in patients with depression(76,79), whereas other studies have reported reduced Bacteroidetes abundance (80,81). These inconsistencies may be related to several factors, including sex differences, variations in the demographic and clinical characteristics of patients, differences in sample size, and the statistical methods used in the studies(81).

Increased levels of *Enterococcus* and *Eggerthella*, bacteria known for their pro-inflammatory effects in the gastrointestinal tract, have also been reported in individuals with depressive disorder(78). Studies have also shown that people with depression often have a higher abundance of Gram-negative bacteria, including genera such as *Oscillibacter*, *Parabacteroides*, *Klebsiella*, *Paraprevotella*, *Veillonella*, *Desulfovibrio*, and *Parasutterella*. These bacteria contain lipopolysaccharides (LPS) in their outer membrane, which can activate the immune system and promote the production of pro-inflammatory cytokines. Since inflammation plays an important role in the pathophysiology of depression, these microbial alterations may contribute to the development of the disorder(82).

In addition to promoting inflammation, dysbiosis may also impair the abundance of beneficial taxa involved in metabolic and neuromodulatory functions. For example, patients with depression often exhibit reduced levels of *Bifidobacterium*. This genus is known to synthesize several B-group vitamins, including riboflavin, niacin, and folate. decreased folate levels can lead to increase in homocysteine, thereby activating NMDA receptors(83). This hyperactivation of NMDAr leads to downregulation of synaptic proteins, impairing neural plasticity in specific neural circuits and lead to chronic exicotoxicity(84). Moreover, certain Bifidobacterium species are capable of producing gamma-aminobutyric acid (GABA), an important neurotransmitter involved in mood regulation. Experimental studies on mice further suggest that specific Bifidobacterium strains may exert antidepressant-like effects by regulating gut 5-hydroxytryptophan (5-HTP) synthesis, increasing serotonin and brain-derived neurotrophic factor (BDNF) levels, and reducing stress-related corticosterone(85–87).

Overall, microbial alterations in patients with MDD manifesting in depletion of anti-inflammatory butyrate-producing bacteria (Faecalibacterium, Coprococcus) and enrichment of pro-inflammatory bacteria (Eggerthella) as well as decreased abundance of microbes involved in neurotransmitter regulation (Bifidobacterium), may collectively influence immune responses, HPA axis activity and neurotransmitter signaling.

4.2 Intestinal Barrier Dysfunction and Peripheral Inflammation

The intestinal barrier is a complex system that maintains host homeostasis by allowing the absorption of nutrients from the gut lumen into the bloodstream while at the same time, preventing the translocation of potentially harmful microorganisms and their components into the bloodstream(88). Structurally, the intestinal barrier consists of a mucus layer and a layer of epithelial cells interconnected by tight junctions. Tight junctions act as a barrier that prevents bacteria and their products from crossing the epithelium but also maintain the proper organization of proteins on the surface of epithelial cells. Epithelial cells together with the mucus layer create a multilayer barrier that separates the host from gut microbiota and limits the passage of bacteria and their antigens from the intestinal lumen into circulation(89,90).

Many factors, including diet, medications, alcohol, stress, infections, and metabolic disorders, may disrupt intestinal barrier homeostasis and increase intestinal permeability. This condition, commonly referred to as “leaky gut,” allows microorganisms, antigens, and toxins to pass into the systemic circulation, triggering inflammatory responses. Increased intestinal permeability has been implicated in several disorders, including major depressive disorder(91). Multiple

studies suggest that intestinal dysbiosis, particularly the loss of beneficial bacterial species, may contribute to epithelial barrier dysfunction(92). These alterations in gut microbiota composition may impair intestinal barrier integrity, leading to increased intestinal permeability and facilitating the translocation of bacterial products, such as lipopolysaccharides (LPS), into the systemic circulation(93). Lipopolysaccharides (LPS) are structural components of the outer membrane of Gram-negative bacteria and consist of a hydrophobic lipid A region and a hydrophilic polysaccharide component. Under physiological conditions, LPS present in the gut lumen do not cross the intact intestinal epithelium. However, disruption of tight junctions and increased intestinal permeability allow LPS to translocate across the intestinal barrier and enter systemic circulation. This process may lead to immune activation and inflammatory responses (94). After entering the bloodstream, LPS act as a pathogen-associated molecular pattern (PAMP) and binds to Toll-like receptor 4 (TLR4) on immune cells, thereby stimulating the production of pro-inflammatory cytokines, including IL-1, IL-6, and TNF-α. Peripheral pro-inflammatory cytokines can influence the central nervous system by inducing microglial activation and production of pro-inflammatory cytokines in the brain, ultimately leading to neuroinflammation. Moreover, LPS can influence neurotransmitter balance thereby affecting mood. In particular, LPS-induced inflammation has been shown to decrease serotonin (5-HT) and dopamine (DA) levels while increase norepinephrine levels(95–97). Studies in animal models further support the role of LPS in the development of depression-like behaviors. In particular, intracerebroventricular injection of LPS in mice resulted in dendritic atrophy in the prefrontal cortex and hippocampal pyramidal neurons and increased levels of pro-inflammatory cytokines such as IL-1β and TNF-α in the hippocampus. These inflammatory changes were associated with neuronal damage and the development of depressive-like states in behavioral tests(97). These findings highlight that impaired intestinal barrier integrity, often resulting from gut dysbiosis, may promote peripheral inflammation and subsequent neuroinflammation, processes that have been strongly associated with the development of depression.

4.3 Neuroinflammation

Neuroinflammation has emerged as an important component of several neurological and psychiatric disorders, including depression(98,99). This process is understood as an inflammatory response occurring within the central nervous system (CNS), primarily mediated by activation of glial cells, especially microglia. Positron emission tomography (PET) studies further support this concept, demonstrating elevated levels of translocator protein (TSPO), a marker of microglial activation, in several brain regions of patients with major depressive

disorder, including the anterior cingulate cortex, prefrontal cortex, hippocampus, and insula- areas involved in emotional regulation and cognitive processing(98).

Microglia are resident immune cells of the central nervous system that regulate brain homeostasis. Upon activation by PAMPs and DAMPs (pathogen- and damage-associated molecular patterns) via TLR receptors, microglia release pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, thereby driving neuroinflammatory processes(8,99). This cytokine production can directly affect brain functions leading to depressive-like symptoms including fatigue ,insomnia, low mood and apetite change. For instance, TNF- α released in response to microglial activation has been associated with hippocampal degeneration, which is commonly observed in patients with depression. Furthermore, IL-6, TNF- α and IFN-γ also activate indoleamine 2,3-dioxygenase (IDO), promoting the kynurenine pathway of tryptophan metabolism. This shift reduces serotonin availability and generates neuroactive metabolites that may alter proper neurotransmittion(100). Disturbances in tryptophan metabolism pathway, particularly reduced serotonin (5-HT) is considered as important factor in the development of MDD(101). Alterations in gut microbiota may further modulate this pathway, therby promoting kynurenine metabolites, kynurenic acid (KYNA) and quinolinic acid (QUIN). These compounds regulate the activity of NMDA receptors involved in synaptic plasticity. Excessive activation of this pathway may lead to neurotoxicity and has been associated with depressive symptoms(102). Additionally, alterations in gut microbiota may further modulate these processes, both by promoting peripheral inflammation due to LPS translocation and through the microbial metabolites like SCFAs, which can cross BBB and directly modulate microglial maturation, metabolism and inflammatory responses(103). For instance, increased abundance of LPS-producing bacteria, may drive neuroinflammation through activation of the complement system, particularly C3. In a CUMS model, this led to enhanced microglial activation and excessive C3-CR3-dependent synaptic pruning in the prefrontal cortex, accompanied by reduced synaptic protein expression (e.g., SYN, PSD95) and the emergence of depressive-like behaviors(104).

4.4 HPA Axis- the link between MGBA and depression

Chronic stress is widely recognized as an important risk factor for the development of depression. Prolonged exposure to stress can lead to persistent activation of the HPA axis, resulting in dysregulation of the stress response system. Under physiological conditions, cortisol exerts negative feedback on the HPA axis to maintain homeostasis; however, in individuals with major depressive disorder (MDD), this regulatory mechanism is often

impaired(105). As a consequence, sustained HPA axis activation leads to increased cortisol levels, which have been observed in patients with depression. Chronically elevated cortisol may contribute to neuroinflammation, increased oxidative stress, and structural alterations in key brain regions involved in emotional regulation(106).

The hippocampus appears to be particularly vulnerable to prolonged exposure to glucocorticoids. These changes have been associated with hippocampal atrophy, together with reduced volume, neuronal loss and dendritic atrophy. Similar alterations have been reported in the amygdala, where chronic stress may induce functional atrophy and impair emotional processing. Collectively, these changes within the limbic system contribute to cognitive deficits and emotional dysregulation- characteristic symptoms of depression. Chronic stress and sustained activation of the HPA axis have also been linked to reduced levels of brain-derived neurotrophic factor (BDNF) in the hippocampus and prefrontal cortex in patients with MDD. Decreased BDNF may lead to long-lasting impairments in synaptic plasticity, contributing to persistent structural and functional changes in the brain. Activation of the HPA axis also affects the serotonergic system. Chronic activation may increase the number of serotonergic receptors in the hippocampus, amygdala, and prefrontal cortex-regions involved in emotional regulation and cognitive processes, leading to disturbances in serotonin signaling. Moreover, elevated cortisol has been shown to increase the expression of the gene encoding the serotonin transporter, resulting in enhanced serotonin uptake by peripheral blood lymphocytes. In addition, glucocorticoids induce the activation of tryptophan 2,3-dioxygenase (TDO), an enzyme that redirects tryptophan metabolism from serotonin synthesis toward the kynurenine pathway, further reducing serotonin availability. This leads to reduced serotonin availability in the brain, which may impair mood regulation(105,107).

Chronic stress may also affect communication within the microbiota-gut-brain axis. Elevated cortisol levels have been associated with alterations in gut microbiota composition, leading to increased intestinal permeability and microbiota- induced peripheral inflammation(58,108). As a result, bacterial components, such as LPS, can translocate through the compromised intestinal barrier into the circulation, thereby inducing the production of pro-inflammatory cytokines, including IL-1, IL-6, and TNF-α. These cytokines may cross the blood-brain barrier and further activate the HPA axis. Moreover, they can impair blood-brain barrier integrity by reducing the expression of tight junction proteins, such as claudin-5, thereby increasing its permeability(60,109).

Taken together, dysregulation of the HPA axis may promote a self-sustaining cycle involving systemic inflammation and alterations in the gut microbiota, thereby exacerbating depressive symptoms and contributing to treatment resistance(108). These interactions highlight the complex interplay between neuroendocrine, immune, and microbial pathways in the pathophysiology of depression.

4.5 Altered Neurotransmission

The pathophysiology of depression is closely linked to disturbances in monoaminergic neurotransmission, particularly involving serotonin, dopamine, and norepinephrine, which are essential for mood regulation(110). However, growing evidence indicates that these changes are also influenced by the gut microbiota. Gut dysbiosis can affect the synthesis and availability of neurotransmitters involved in mood regulation including 5-HT, GABA, dopamine and norepinephrine. However, alterations in these signaling pathways in patients with depression, may in turn influence microbial composition, highlighting a bidirectional relationship within gut-brain axis(68).

The serotonergic system has long been implicated in the pathophysiology of depression, with evidence showing that reduced tryptophan availability leads to decreased serotonin synthesis and may precipitate depressive symptoms, particularly in vulnerable individuals. Consistently, alterations in serotonin (5-HT) synthesis, release, and reuptake are commonly observed in depression and may be further influenced by gut dysbiosis through disrupted tryptophan metabolism(102,110).

Tryptophan is an essential amino acid and a precursor of serotonin. However, approximately 90% of it is metabolized via the kynurenine pathway through the activity of tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO). This results in producing kynurenine and its downstream metabolites- quinolic acid (QA) and 3-hydroxykynurenine (3-HK)(102). Recent evidence suggests that gut microbiota plays a vital role in modulating these processes. Gut dysbiosis has been shown to shift tryptophan metabolism away from serotonin synthesis toward the kynurenine pathway, resulting in increased production of metabolites such as kynurenine, quinolinic acid (QA), and 3-hydroxykynurenine (3-HK). At the same time, dysbiosis may compromise intestinal barrier integrity and promote a state of low-grade systemic inflammation, which is frequently observed in patients with depression(111). This inflammatory response, driven by factors such as lipopolysaccharide (LPS) translocation, leads to increased production of pro-inflammatory cytokines, which can activate IDO and promote

kynurenine pathway activity(112). This shift has important consequences for neuroplasticity. Metabolites of the kynurenine pathway, particularly quinolinic acid (QUIN), exhibit neurotoxic properties. Acting as an NMDA receptor agonist, QUIN can reduce brain-derived neurotrophic factor (BDNF) expression, while other neurotoxic metabolites may further disrupt glial-neuronal interactions involved in neurotrophic support. In addition, reduced BDNF levels may further enhance activation of the neurotoxic branch of the kynurenine pathway, especially under chronic stress conditions(113).

Under normal conditions, SCFAs, particularly butyrate, may inhibit IDO activity and help maintain the balance between serotonin and kynurenine pathways. However, dysbiosis-associated reductions in SCFA production can remove this inhibitory effect, leading to excessive IDO activation and further shifting tryptophan metabolism toward the kynurenine pathway. Furthermore, reduction in SCFAs may lead to decreased BDNF levels and impaired neuroplasticity(111).

Gut dysbiosis may also affect GABAergic neurotransmission. GABA is the main inhibitory neurotransmitter in the central nervous system and plays an important role in regulating mood, memory, and stress responses, with well-documented anxiolytic effects(114). Reduced GABA levels have been observed in patients with depression, as well as in other conditions such as sleep disorders, anxiety, multiple sclerosis, and irritable bowel syndrome. Certain gut bacteria, including *Lactobacillus* and *Bifidobacterium,* are capable of producing GABA and may influence mood through signaling pathways involving the enteric nervous system and the vagus nerve. Consequently, gut dysbiosis may impair this process by reducing the abundance of GABA-producing bacteria, leading to decreased GABA availability(95,115).

Dopamine is involved in motivation, reward processing, and motor function, and its dysregulation is closely associated with core depressive symptoms such as anhedonia, fatigue, and reduced motivation(95). Gut dysbiosis may contribute to these alterations by affecting both dopamine synthesis and neuronal function. Changes in microbiota composition have been linked to reduced availability of dopamine precursors, for example through depletion of genera such as *Coprococcus,* which are involved in the production of DOPAC, a dopamine metabolite(116). Moreover, dysbiosis is often associated with increased intestinal permeability, which facilitates the translocation of lipopolysaccharide (LPS) into the circulation. This, in turn, promotes systemic inflammation that may negatively affect dopaminergic neurons. Chronic exposure to LPS has been shown to reduce dopamine levels, likely through neuroinflammatory and neurodegenerative mechanisms, as well as altered dopamine turnover(95). Experimental

studies show that gut dysbiosis can alter dopaminergic signaling, including changes in striatal dopamine turnover accompanied by behavioral abnormalities. Importantly, these changes may be partially reversed following microbiota transfer, suggesting a direct link between gut microbial composition and dopamine-related pathways(117).

Conclusions

As discussed in this review, gut dysbiosis may contribute to depression through disturbances within the microbiota-gut-brain axis. Alterations in gut microbiota composition can impair intestinal barrier integrity, leading to increased permeability and facilitating the translocation of bacterial components, such as LPS, into the circulation. These processes may trigger systemic and neuroinflammatory responses. At the same time, dysregulation of the hypothalamic-pituitary-adrenal axis, driven by dysbiosis, can further disrupt MGBA signaling and affect brain function. Gut dysbiosis may also contribute to disturbances in neurotransmission, affecting the balance of neurotransmitters involved in mood regulation. Microbiota-derived metabolites may additionally play a role in these processes, as they can influence multiple pathways involved in gut-brain communication. Importantly, these mechanisms are closely interconnected and may reinforce one another, creating a self-perpetuating cycle of inflammation, barrier dysfunction, and altered gut-brain signaling that may underlie the persistence of depressive symptoms. Notably, approximately 30% of patients with depression do not respond adequately to standard treatment, highlighting the need to better understand microbiota-gut-brain-axis-related mechanisms. In this context, the gut microbiota represents a promising target for future therapeutic strategies. Nevertheless, further research is required to better understand the causal relationship between gut microbiota and depression, as well as to develop effective microbiota-based interventions.

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Conceptualization: Julia Lorek, Katarzyna Szeliga

Methodology: Julia Lorek, Katarzyna Szeliga, Magda Sawin

Formal Analysis: Magda Sawin, Patrycja Waszkiewicz

Investigation (literature search and screening): Magda Sawin, Patrycja Waszkiewicz, Jakub Korybski

Data Curation: Patrycja Waszkiewicz, Jakub Korybski, Wiktoria Brzozowska

Writing- original draft preparation: Julia Lorek, Magda Sawin

Writing- review and editing: Katarzyna Szeliga, Jakub Korybski, Wiktoria Brzozowska, Hanna Jabłońska, Franciszek Jabłoński, Daniel Grobecki, Adam Jarczak

Visualization: Wiktoria Brzozowska, Hanna Jabłońska

Supervision: Julia Lorek

Project administration: Katarzyna Szeliga

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