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MAJOR DEPRESSIVE DISORDER AND THE MICROBIOME-GUT-BRAIN AXIS

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The central nervous system and the gastrointestinal tract are connected bidirectionally via the gut-brain axis (GBA). According to the gut microbiota hypothesis, changes in the composition and activity of the gut microbiota can affect the GBA, contributing to the onset of mental illnesses such as depression and anxiety. This review aims to analyze how microbiota imbalances can affect the functioning of the gut-brain axis, causing changes in metabolism, immune system and neurotransmitters that are associated with depression. The potential of dietary modifications, probiotics, prebiotics and symbiotics to restore microbiota balance as well as the importance of microbiota profiling integration into personalized clinical practice are discussed.

K e y w o r d s: microbiota-gut-brain axis, major depressive disorder, probiotics, dietary pattern, personalized treatment.

The human body is a complex biological system comprised of various organs, tissues, and fluids that interact dynamically through circulatory, nervous, and endocrine systems to maintain homeostasis. Among these systems, the gastrointestinal tract and its associated microbiota have emerged as key players in modulating systemic and mental health. This emerging field focuses on the Gut-Brain Axis (GBA) and its connection to the gut microbiome's role in mental disorders. The colonization of the gut by microbes begins in utero, with microbes found in the placenta, umbilical cord, and amniotic fluid, achieving equilibrium and peak diversity by two years of age [1]. In recent studies, the gut microbiota is known as a key component in health and disease, and often referred to as the "second brain". It owes this designation to the enteric nervous system (ENS), a vast network of neurons embedded in the gastrointestinal wall that operates semi-autonomously while engaging in bidirectional communication with the central nervous system (CNS) [2-4]. The gut microbiota, consisting largely of bacteria, archaea, fungi, and viruses, plays critical roles in immunity, signaling, and metabolism. Communication between the gut microbiota and the brain occurs via the ENS, the vagus nerve, and immune pathways, forming the basis of the bidirectional GBA. This system influences emotional and cognitive behaviors by connecting the CNS to peripheral intestinal activities [5].

The DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) and the ICD-11 (International Classification of Diseases, 11th Revision) are the most definitive resource for the classification, diagnosis, and treatment of mental disorders. In this review, we specifically focus on major depressive disorder (MDD), classified under code F32-F33 in ICD-11 and as 296.xx in DSM-5. MDD is a mental disorder that causes a persistent feeling of sadness or loss of interest, anhedonia, cognitive disturbances, changes in appetite or sleep, and feelings of worthlessness, which significantly impair daily functioning. The etiology of MDD is multifactorial, involving genetic predisposition, neurobiological dysfunction (including neurotransmitter imbalances), chronic inflammation, hypothalamic pituitary adrenal (HPA) axis dysregulation, and psychosocial stressors [6, 7].

Mental health is largely impacted by gut microbiota, influencing stress, anxiety, and mood regulation. Studies indicate that probiotics and prebiotics may offer therapeutic potential in addressing stress-related mental health issues, although further research is needed to fully unravel the complexities of gut-brain interactions [8]. The GBA enables a

reciprocal relationship, where gut microbiota impacts mental health through immune, endocrine, and metabolic pathways, while the brain regulates gut functions such as appetite and energy metabolism [5]. In individuals with depression, gut-brain disruptions often include imbalanced gut microbiota, gastrointestinal issues, and altered metabolic and appetite regulation [3]. Depression is characterized by chronic sadness and a loss of interest in activities, significantly impairing daily life. The gut microbiota's ability to mitigate inflammation and oxidative stress underscores its importance in improving depressive symptoms [9]. Maintaining a balanced microbiota is essential for mental well-being.

MDD affecting one in five people worldwide, is the leading global cause of disability. MDD is a complex condition influenced by genetic, stress-related, social, and pathological factors, manifesting in symptoms like immune dysregulation, gut-brain axis abnormalities, and the HPA axis disruptions. Stress, for example, suppresses serotonin (5-HT) production, while the HPA axis, immune system, and gut microbiota collectively influence serotonin regulation, which is central to MDD symptomology [10]. Traditional treatments for depression, including pharmacotherapy (e.g., SSRIs, SNRIs) and psychotherapy, have shown efficacy but often result in side effects like dependency, withdrawal symptoms, weight gain, and emotional blunting. Additionally, 40% of individuals with depression do not seek treatment, and of those who do, many receive suboptimal care [11, 12]. These drawbacks necessitate alternative approaches to reduce medication side effects and improve adherence, including dietary interventions and microbiota-targeted therapies such as probiotics, prebiotics, and symbiotics, which have shown promise in modulating gut-brain interactions and reducing depressive symptoms [13].

Emerging evidence highlights the impact of diet on gut microbiota composition and GBA function, influencing depression's onset and treatment. Nutritional interventions, such as Mediterranean and Japanese diets, show promise in preventing and alleviating depressive symptoms [14, 15]. Mind-body therapies like mindfulness-based cognitive therapy have also demonstrated potential in modifying microbiota composition and improving GBA function [16]. Probiotics and prebiotics have shown therapeutic potential, with prebiotics reducing depressive symptoms and probiotics mitigating stress responses and altering emotional biases. Key nutrients, including zinc, vitamin D, folate, and omega-3 fatty acids, play pivotal roles in GBA function and mental health. Dietary therapies incorporating these nutrients, along with probiotics and prebiotics, may offer effective strategies for depression prevention and management. However, further research is needed to refine these approaches and establish optimal dietary interventions for mental health.

This review aims to elucidate the mechanisms through which the microbiota-gut-brain axis influences mental health and to evaluate the impact of dietary patterns and microbiota-targeted therapies on depression. Additionally, it seeks to provide a comprehensive framework for understanding the MGBA's role in mental health and its potential as a therapeutic target for major depressive disorder.

Gut-brain axis and mental health

The central nervous system and the gastrointestinal tract are connected bidirectionally via the GBA. This complicated system involves signaling pathways that regulate the immune system, hormones, and the neurological system. Over recent decades, the role of the GBA in mental health has gained significant attention. Research indicates that the gut microbiome plays a crucial role in influencing the GBA, thereby impacting mental health outcomes. Reported studies have highlighted that dietary choices significantly affect the composition of the gut microbiota, which in turn influences GBA functionality. Understanding the mechanisms behind the GBA and its connection to mental health may lead to innovative strategies for preventing and treating psychological disorders.

According to the gut microbiota hypothesis, changes in the composition and activity of the gut microbiota can influence the GBA, contributing to the onset of MDD and generalized anxiety disorder (GAD), which are categorized as mental and behavioral disorders in the DSM-5 and ICD-11 [2, 6, 7]. These changes may include reduced microbial diversity, depletion of beneficial species (e.g., *Lactobacillus, Bifidobacterium*), and overgrowth of pro-inflammatory taxa (e.g., *Desulfovibrio, Clostridium*) – can impair GBA signaling and contribute to psychiatric symptoms [17, 18].

This disruption occurs through multiple pathways, including immune system activation (via pro-inflammatory cytokines), modulation of neurotransmitter levels (such as serotonin and GABA), regulation of the HPA axis, and the production of

key microbial metabolites like short-chain fatty acids (SCFAs) [19-22]. By modulating these systems, certain probiotics (e.g., *Lactobacillus helveticus* R0052, *Bifidobacterium longum* R0175) and prebiotics (e.g., galactooligosaccharides (GOS), fructooligosaccharides (FOS)) have shown promising effects in alleviating symptoms of anxiety and depression. A subset of probiotics and prebiotics known as psychobiotics may serve as effective adjunct therapies for mood disorders by restoring microbial equilibrium and reducing systemic inflammation [23, 24].

One primary mechanism by which the gut microbiome influences the GBA is through the production of neurotransmitters, including serotonin (5-HT), dopamine, and GABA. These neurotransmitters are vital for mood and behavioral regulation. For instance, *Lactobacillus rhamnosus* modulates GABA receptor expression in the brain via vagal pathways [19]. Animal models have shown that disruptions in gut microbiota lead to altered neurotransmitter levels, which are linked to symptoms of anxiety and depression. Additionally, the gut microbiota plays a role in regulating the HPA axis, a central component of the stress response. Dysregulation of the HPA axis has been implicated in the development of anxiety and depression [25]. Another study reported that *Blautia*, *Coprococcus*, and *Bifidobacterium* were more abundant in patients with MDD who responded positively to treatment, showing a positive association with the efficacy of SSRI antidepressants [26]. It has been found that SCFAs elevate 5-HTP levels by promoting the expression of Tph1 *in vitro* [27]. This suggests that sustaining high levels of serotonin precursors may strengthen the antidepressant effects of SSRIs [28].

The microbiome exerts a broad influence on host physiology, including nutrient metabolism, immune system development, and resistance to infections. It also affects neuroinflammation, brain injury responses, and neurogenesis by modulating peripheral immune cells. The interactions between the immune system and gut microbiota have been implicated in the etiology of mental disorders, particularly depression [29]. This complex interplay underscores the microbiota's role in regulating brain function and its connection to mental health. A strong link between gut microbiota disturbances and depressive-like behaviors has been suggested. Co-morbidity between depression and gastrointestinal disorders is well-documented, with gut microbiota imbalances often accompanying depressive symptoms. Stress has been shown to cause long-lasting changes in the diversity and composition of gut microbiota, further contributing to depressive symptoms. Conversely, prebiotics have demonstrated antidepressant properties in several double-blind, placebo-controlled trials, as well as in animal and human studies [30]. These findings highlight the therapeutic potential of targeting the gut microbiota in mental health interventions.

Probiotics and prebiotics represent promising treatment options for anxiety and depression. Probiotics, which are live bacteria that confer health benefits, have been shown to maintain gastrointestinal homeostasis by competing with pathogenic bacteria, potentially improving mood and behavior. Probiotic supplementation has also demonstrated efficacy in enhancing cognitive performance and reducing symptoms of anxiety and depression in individuals. Prebiotics, on the other hand, act as specific plant fibers that promote the growth of beneficial bacteria in the gut. These compounds have shown potential in treating anxiety and depression through their ability to support a healthy gut microbiota [25].

In summary, the gut-brain axis is a critical mediator of the relationship between gut health and mental health. The microbiome influences the GBA through neurotransmitter production, immune system modulation, and stress response regulation, making it a potential target for treating mental health disorders such as anxiety and depression. Probiotics and prebiotics offer viable therapeutic strategies, emphasizing the importance of maintaining a balanced gut microbiota for optimal mental health outcomes.

Gut-brain axis and its modulation in anxiety and depression

In humans, the gastrointestinal tract is predominantly colonized by bacteria from the *Firmicutes* and *Bacteroidetes* phyla, with smaller contributions of *Actinobacteri*a, *Verrucomicrobia*, *Proteobacteria*, *Fusobacteria*, and *Cyanobacteria* [31]. Factors such as delivery mode (vaginal vs. cesarean), breastfeeding, nutrition, medication use (especially antibiotics), exposure to infections, and environmental stressors like smoking shape and modify the microbiota throughout life [32]. The gut microbiota interacts with the brain through multiple pathways, including the HPA axis, neuroendocrine signals, autonomic responses, and neuroimmune mechanisms [30]. Neurotransmitters such as norepinephrine (NE), epinephrine (E), dopamine (DA), and serotonin are critical regulators of gut physiology. These

molecules influence gut motility, nutrient absorption, immune responses, and blood flow. Emerging evidence has linked disturbances in these neurotransmitters to gastrointestinal and CNS disorders, further underscoring their importance in GBA functionality.

Gut permeability and proinflammatory environments are also implicated in mood disorders such as anxiety and depression [33]. Altered gut microbiota composition may exacerbate systemic inflammation, contributing to the development of inflammation-related diseases in individuals with a history of mood disorders. Studies suggest that the bidirectional communication facilitated by the GBA and the microbiota impacts both mental and physical health, highlighting the interdependence of these systems.

Neurological disorders, including Parkinson's disease and inflammatory bowel disease (IBD), further illustrate the interplay between the GBA and neurotransmitter dysregulation. These conditions often involve gastrointestinal disturbances and are associated with increased intestinal permeability, which fosters a proinflammatory environment [33, 34]. Such findings underscore the role of gut health in regulating inflammation and its subsequent impact on mental health.

The microbiome's role in regulating behavior and mood has attracted attention as a potential target for therapeutic interventions. Modulating the gut microbiota using probiotics, prebiotics, or symbiotics could offer novel approaches for treating anxiety and depression. These strategies may help restore microbial equilibrium, enhance GBA function, and improve mental health outcomes. However, further research is required to clarify the mechanisms underlying microbiome-GBA interactions and to develop effective microbiome-based therapies for mental health disorders. Growing evidence also suggests that the gut microbiota may influence the effectiveness of conventional psychotropic drugs. For example, Cussotto et al. investigated how common antidepressants, including the SSRI paroxetine, affected the gut microbiome in rodent models. They found that paroxetine treatment altered the composition of the gut microbiota and impacted gastrointestinal function, indicating a bidirectional relationship in which SSRIs can modify the microbiome, and the microbiome may, in turn, influence SSRI metabolism and efficacy. These findings highlight the importance of considering gut microbiota composition in the therapeutic use of SSRIs for MDD [35]. Specific gut microorganisms produce enzymes such as β-glucuronidase and other xenobiotic-metabolizing proteins, which can alter the chemical structure or deconjugate SSRIs, potentially influencing their systemic availability and pharmacological activity [36]. Additionally, disturbances in gut microbiota composition, referred to as dysbiosis, may impair SSRI absorption by modulating factors such as gastrointestinal pH, bile acid profiles, and the integrity of the intestinal mucosal barrier [37, 38]. SSRIs themselves have been shown to reshape the gut microbial environment, reducing microbial diversity and potentially disrupting community stability, which could contribute to therapeutic resistance or unwanted side effects [39]. A deeper understanding of these bidirectional interactions may pave the way for microbiota-informed treatment approaches, enhancing antidepressant efficacy while preserving or even improving gut health. These insights highlight the promise of microbiota-targeted strategies to improve pharmacological outcomes and support personalized interventions in mental health care.

A personalized strategy for modulating the gut microbiota using probiotics, prebiotics, or symbiotics is a new approach to the treatment of anxiety and depression. These strategies aim to tailor microbiota interventions to individual microbial profiles, genetics, lifestyle factors, and treatment history. Key components include microbiota profiling (via 16S rRNA or metagenomic sequencing), identification of microbial deficits or pro-inflammatory overgrowths, use of targeted probiotics, prebiotics, or symbiotics to correct imbalances, as well as integration with standard psychiatric care to enhance efficacy. For example, individuals with low *Bifidobacterium* levels may benefit from *Bifidobacterium longum* supplementation, while those with stress-related HPA dysregulation might respond to *Lactobacillus rhamnosus* strains that influence GABA receptors [23].

The field of psychiatry is increasingly recognizing the significance of the GBA and the microbiome. Advancing our understanding of these interactions could revolutionize the treatment and management of mood disorders, offering innovative solutions that integrate microbiota modulation with existing therapeutic approaches.

The role of gut microbiota in brain function

The gut microbiota is increasingly recognized as a critical factor in regulating brain function and behavior. Studies have demonstrated that alterations

in the gut microbiota can impact brain processes and contribute to the development of various mental health conditions [40, 41]. For instance, Jiang et al. analyzed fecal samples from patients with MDD and found a reduced abundance of certain beneficial taxa (e.g., *Faecalibacterium* and *Bifidobacterium*) and an increased abundance of potentially detrimental bacteria (e.g., *Alistipes*), suggesting a distinct microbial signature associated with depression [41]. The bidirectional connection between the gut microbiota and the brain is mediated by mechanisms such as neurotransmitter synthesis, immune system activation, and regulation of the HPA axis [19, 42]. Gut microbiota also influences several key pathways, including the formation and activity of immune cells involved in brain inflammation and neurodegeneration, as well as the production of neurotransmitters and other signaling molecules that regulate brain function. These pathways have significant implications for mental health, particularly in stress responses, anxiety, and mood regulation. Research has linked changes in gut microbiota composition and diversity to stress-related disorders such as depression, anxiety, and post-traumatic stress disorder (PTSD) [19, 43-45].

Preclinical studies using mouse models suggest that probiotics and prebiotics can improve behavior and mental health outcomes, including alleviating anxiety and depression-like symptoms. These findings indicate the potential for microbiome-based interventions as novel treatment strategies for stress-related psychiatric conditions [46, 47]. Emerging evidence also supports the role of microbiota in central nervous system disorders, with microbiome-based therapies showing promise for conditions such as anxiety and depression [23, 48].

Through the microbiota-gut-brain axis (MGBA), the gut microbiota controls brain function by affecting immunological signals, neurotransmitters, SCFAs, and the HPA axis. Reduced microbial diversity, increased gut permeability, inflammation, and disturbed neurotransmitter synthesis are all associated with mental illnesses such as MDD, GAD, and PTSD. Vagal activation, immunological modulation, SCFA synthesis, and bacterial manufacture of serotonin and GABA are important processes. By increasing SCFA synthesis, decreasing inflammation, and restoring neurotransmitter balance, psychobiotic interventions, such as probiotics (like *Lactobacillus* and *Bifidobacterium* strains) and prebiotics (such GOS, FOS), show promise in lowering stress, anxiety, and depression. Personalized microbiota-based psychiatric therapies require more investigation [19, 43, 44].

Alterations in the gut microbiota have been associated with a range of mental health disorders, including depression, anxiety, and autism spectrum disorders [49]. For example, studies have shown that changes in the gut microbiota can induce depressive-like behaviors in animal models. Additionally, Mason et al. found that individuals with depression and anxiety disorders exhibit distinct gut microbiota profiles compared to healthy controls, further suggesting the microbiota's involvement in the pathophysiology of depression [50]. These findings highlight the potential of targeting the gut microbiota as a preventative and therapeutic approach for mental health disorders.

In summary, the gut microbiome plays a pivotal role in brain function and mental health by regulating mood and behavior through bidirectional communication. Interventions targeting the gut microbiota, such as probiotics and prebiotics, offer a promising strategy for addressing mental health issues related to stress and other psychological disorders. However, further research is needed to fully elucidate the intricate relationships between the gut microbiota and the brain and to develop effective microbiome-based therapies for individuals with mental health conditions.

The link between gut dysbiosis and depression

Gut dysbiosis is an imbalance in the composition of the gut microbiota that manifests as an overabundance of pro-inflammatory bacteria and the loss of beneficial species like *Bifidobacterium* and *Faecalibacterium prausnitzii*. MDD results from neuroinflammation and compromised neurotransmission, through processes including altered tryptophan metabolism, pro-inflammatory cytokine activation, dysregulation of the HPA axis, and increased intestinal permeability [5, 51, 52].

Growing evidence highlights the role of the commensal gastrointestinal (GI) microbiota in influencing behavior and gut function. Studies show that antibiotic-induced dysbiosis affects brain chemistry and behavior, increasing the risk of depression. While antibiotics are critical in treating infections, they disrupt the microbiota-gut-brain axis by eliminating both pathogenic and beneficial microbes. This disruption is associated with dose- and time-dependent risks of depression and anxiety, persisting for years after antibiotic use [53-55]. Stress

further exacerbates microbiota changes, impacting gut barrier function and neurotransmitter regulation, with early-life and adulthood stressors contributing to dysbiosis and subsequent mental health issues [56, 57].

Diet also significantly influences the gut microbiota, with poor nutrition increasing the risk of depression. Diets such as cow milk formula or the Western diet, characterized by high sugar and fat intake and low fiber, disrupt microbial balance and promote gut dysbiosis, impacting long-term health [58, 59].

The bidirectional relation between the IBD and depression. IBD, including Crohn's disease and ulcerative colitis, is associated with a high prevalence of depression, with disease activity and inflammation contributing to depressive symptoms [60]. Chronic inflammation in IBD produces pro-inflammatory cytokines that impact mood regulation and cognitive function. Dysbiosis and gut-brain axis dysfunction are common features in both IBD and depression, suggesting shared mechanisms such as immune dysregulation and altered neurotransmitter function [61-63].

IBD and depression have a bidirectional connection; stress and depression worsen the IBD flares, and up to 40% of the IBD patients have depressive symptoms. The gut-brain-microbiota axis, which involves interactions between immunological activation, neurotransmitter disruption, and dysbiosis, mediates this relationship [64, 65]. IBD damages brain function and the integrity of the intestinal barrier by reducing good bacteria that produce butyrate, such as *Faecalibacterium prausnitzii*, which are known to have anti-inflammatory effects [66]. As inflammatory cytokines increase, such as TNF-α and IL-6, they can penetrate the blood-brain barrier, alter neurotransmission, and extend exposure to cortisol [67, 68]. Depression becomes worse by chronic inflammation, which alters tryptophan metabolism, lowers serotonin, and increases neurotoxic kynurenines. Through unhealthy lifestyle choices and physiological stress, depression exacerbates IBD by sustaining inflammation and dysbiosis [52].

Non-pharmacological treatments, including psychotherapy and dietary modifications, have shown promise in addressing the shared pathogenesis of IBD and depression, paving the way for personalized therapies targeting both conditions.

The complex relationship between irritable bowel syndrome (IBS) and depression. IBS, a multifactorial the GI condition, often coexists with depression and anxiety, with up to 30% of the IBS patients experiencing these comorbidities. Altered gut microbiota in IBS patients, characterized by reduced microbial diversity and beneficial bacteria, disrupts gut-brain communication, contributing to both the GI symptoms and depression [69, 70].

Probiotics, prebiotics, and dietary interventions such as the low FODMAP diet have demonstrated efficacy in alleviating the IBS symptoms and improving mood. These treatments work by modulating the gut microbiota and reducing gut inflammation, offering a promising approach for managing IBS with comorbid depression [24, 71, 72].

Obesity and depression: the role of gut dysbiosis. Obesity is a complex metabolic condition driven by genetic, lifestyle, and environmental factors. Although it is not classified as a mental disorder, it is strongly associated with increased rates of depression, and this link is bidirectional: obesity increases the risk of developing depression, while depression can lead to behaviors that promote weight gain [73]. Obese individuals typically have less diverse gut microbiota, which contributes to metabolic disorders such as insulin resistance and type 2 diabetes [63, 74]. They typically have reduced microbial diversity, a higher Firmicutes-to-Bacteroidetes ratio, and an increased abundance of pro-inflammatory taxa such as *Ruminococcus*, *Enterobacteriaceae*, and *Desulfovibrio* [75]. Dysbiosis also impacts brain function and behavior by regulating neurotransmitters like serotonin and dopamine, which are critical for mood and behavior [30].

Short-chain fatty acids (SCFAs), metabolites produced by the gut microbiota, play a role in gut-brain communication by modulating neurotransmitter synthesis and reducing neuroinflammation. These processes are linked to the pathophysiology of both depression and obesity [76].

In summary, gut dysbiosis is a significant factor in the development and management of mental health conditions such as depression, IBD, IBS, and obesity. Obesity, IBD, and IBS are not psychiatric disorders; they are classified as somatic conditions. However, they share a strong comorbid relationship with depression and anxiety, driven by shared inflammatory and neurobiological mechanisms. For example, IBD patients frequently experience depression during disease flares. IBS is highly comorbid with anxiety, often referred to as a "gut-brain disorder". Obesity is associated with both increased

depression risk and treatment-resistant depression in some individuals [64, 77].

Mechanisms of the gut-brain axis in mental health

Over 280 million individuals worldwide suffer from MDD, a complicated illness that the WHO projects will be the primary source of disease burden by 2030 [12]. It arises from biological (e.g., inflammation, gut microbiota changes, neurotransmitter imbalances), psychological (e.g., trauma, cognitive distortions), and social (e.g., stress, isolation). Prolonged stress is important because it triggers the HPA axis and autonomic nervous system, which results in excitotoxicity, neurotransmitter abnormalities, and cortisol dysregulation [78-80]. In addition to contributing to neuroinflammation, elevated pro-inflammatory cytokines (IL-6, TNF-α, and IL-1β) can interfere with mood modulation [81]. Through immunological regulation and microbial metabolites, the gut microbiota also affects depression. Hormonal effects (e.g., estrogen) can also heighten inflammatory responses and stress reactivity, making women more susceptible to MDD [82]. These interrelated processes emphasize the necessity of comprehensive, individualized therapies that address both these interconnected mechanisms, highlight the need for holistic, personalized treatments targeting both brain and gut physiology.

Stress, defined as a perceived threat to equilibrium, activates the stress response, a systemic reaction involving the endocrine, nervous, and immune systems to maintain homeostasis. The HPA axis is central to this response, integrating signals from the hypothalamus, pituitary gland, and adrenal glands. Chronic dysregulation of the HPA axis, often observed in depression, results in elevated cortisol levels, hypercortisolemia, and disrupted cortisol rhythmicity in 40–60% of depressed patients [83, 84]. This overactivation is linked to symptoms such as low mood, appetite loss, and sleep disturbances [85].

Glutamate, the brain's most abundant excitatory neurotransmitter, plays a critical role in synaptic plasticity and cognitive functions. However, inflammation-induced disruptions in glutamate metabolism can lead to excessive extracellular glutamate accumulation, contributing to excitotoxicity and neural damage in depression [86, 87]. Elevated glutamate levels have been observed in the cerebrospinal fluid and blood of depressed patients [88].

The "macrophage theory of depression" highlights the role of immune dysregulation and pro-inflammatory cytokines in MDD. Cytokines are multifunctional proteins that mediate cellular communication and immune responses. Imbalances in cytokine production, with an overactivation of pro-inflammatory cytokines, are associated with mood disorders. Disturbances in leukocyte function and cytokine expression have been proposed as biomarkers for depression and PTSD, with anti-inflammatory drugs showing potential antidepressant effects [89, 90].

Gender differences in immune responses may also contribute to the higher prevalence of inflammatory illnesses and depression in females [92]. Dysfunction in the cortisol feedback mechanism to the glucocorticoid receptor and immune cell receptors further exacerbates cytokine over-secretion, linking immune dysregulation to depression's pathophysiology [83].

In summary, the gut-brain axis mechanisms involved in depression include the HPA axis dysregulation, glutamate-mediated excitotoxicity, and immune system imbalances. These interconnected pathways underscore the multifactorial nature of MDD and provide targets for therapeutic interventions.

Microbiota-gut-brain axis and depression

Depression, a prevalent mental illness, has been linked to changes in gut microbiota composition and function. The MGBA represents a bidirectional communication system involving the gut microbiota, enteric nervous system, and central nervous system, and is increasingly recognized as a key factor in the pathophysiology of depression [2, 40, 76].

The MGBA, which controls mood and cognition, has been connected to changes in gut microbiota in MDD, a prevalent and incapacitating disorder. Diet is important; the Western diet increases the risk of depression, but anti-inflammatory diets like the Mediterranean diet lower it. By increasing SCFA synthesis, decreasing inflammation, reestablishing microbial balance, and boosting neurotransmitter availability, nutritional therapies such as probiotics, prebiotics, and essential nutrients like omega-3s and vitamin D assist in regulating gut-brain transmission [92, 93]. These results demonstrate the potential of microbiota-targeted treatments as depression management adjuncts.

Dietary patterns significantly influence gut microbiota and mental health. Healthy diets like the Mediterranean diet are associated with reduced depression risk, while unhealthy patterns,

such as the Western diet, correlate with increased risk [92, 93]. Nutritional interventions, including probiotics, prebiotics, and essential nutrients like zinc, vitamin D, folate, and omega-3 fatty acids, have demonstrated potential in managing depression by improving MGBA function [24, 94].

The conception of MGBA in depression

Dysbiosis, an imbalance in gut microbiota, has been implicated in depression. Research highlights how probiotics, prebiotics, and fecal microbiota transplantation can modify gut microbiota, influencing behavior and mood [33, 95]. Mechanisms such as neurotransmitter synthesis (e.g., serotonin production), immune system modulation, and the HPA axis regulation link the MGBA to depression [2, 30, 96].

By disrupting neurotransmitters, activating the immune system, and dysregulating the HPA axis, gut dysbiosis, characterized by a decrease in microbial diversity and an increase in pro-inflammatory species, is associated with MDD. Probiotics, prebiotics, and fecal microbiota transplantation (FMT) are examples of microbiota-targeted treatments that may be advantageous. Probiotics, including strains of *Lactobacillus* and *Bifidobacterium*, increase the precursors of GABA and serotonin, decrease cortisol, and lessen inflammation. Prebiotics enhance serotonin synthesis, increase the generation of SCFAs, and support good bacteria. By restoring neurotransmitter levels and lowering inflammation, FMT has demonstrated potential in experimental models and restores microbial diversity [23, 40]. These techniques may be used as supplemental treatments for depression as they alter the gut-brain-microbiota axis.

Overall, the MGBA offers a promising target for novel depression treatments. However, further research is required to fully understand the complex interactions between gut microbiota and mental health.

The impact of gut microbiota composition on depression

Depression is characterized by various dysfunctions, including neurotransmitter imbalances, inflammation, and gut-brain axis disruptions [3, 97, 98]. Gut dysbiosis may underlie these issues, with stress-induced pro-inflammatory cytokine overproduction contributing to depressive symptoms. Antidepressants are known to reduce inflammation and restore gut microbial balance [83, 90, 97, 99, 100] as shown in Table 1.

Some antidepressants, like SSRIs, have antimicrobial effects, targeting specific bacteria and helping restore microbiota balance. However, long-term use may also disrupt gut flora, highlighting the need for targeted therapies that consider microbiota composition [101, 102] as shown in Table 1.

The effects of probiotics and prebiotics on depression

Probiotics and prebiotics, collectively known as symbiotics, can modulate gut microbiota and improve mental health as shown in Table 2. Probiotics have shown efficacy in reducing depressive symptoms in patients with MDD and healthy individuals by modulating gut flora and emotional responses [13, 106]. Prebiotics indirectly enhance mental health by encouraging the growth of beneficial bacteria and reducing cortisol levels [24].

FMT has also demonstrated potential in treating depression by restoring microbial balance and improving depressive-like behaviors [52]. Dietary changes, including increased fiber intake and fermented foods, can similarly improve gut microbiota composition and mental health outcomes as shown in Table 2 [107].

The role of dietary patterns in depression and the MGBA

Diet plays a significant role in depression management as shown in Table 3. The Mediterranean diet, characterized by high consumption of plant-based foods, healthy fats, and limited red meat, has been linked to reduced depression risk [108]. Similarly, the traditional Japanese diet, emphasizing vegetables, fish, and soy products, is associated with decreased depressive symptoms [14].

Modified Mediterranean diets and traditional Japanese diets have been shown to influence gut microbiota composition, reducing inflammation and depressive symptoms [109, 110]. These dietary patterns highlight the potential of nutritional strategies in managing depression through MGBA modulation.

In summary, the MGBA plays a vital role in the pathophysiology of depression, with dysbiosis contributing to its onset and severity. Nutritional interventions, including probiotics, prebiotics, and healthy dietary patterns such as the Mediterranean and Japanese diets, offer promising therapeutic avenues. Further research into the MGBA's mechanisms and its influence on mental health is essential for developing effective microbiota-targeted therapies for depression.

Table 1. Positive and negative effects of gut microbiota modulation in depression

Aspect	Positive effects	Negative effects
Gut-brain axis disruption	Potential for therapeutic targeting to restore balance [3, 97, 102]	Disruptions linked to neurotransmitter and HPA axis imbalances [3, 97, 102]
Inflammation and depression	Anti-inflammatory properties of antidepressants reduce cytokines [99]	Chronic inflammation exacerbates depressive symptoms [99, 103]
Antidepressant modulation	Modulates cytokine levels, enhancing anti-inflammatory responses [83, 100]	Potential adverse effects if cytokine modulation is not targeted effectively [104]
Psychotropic medications	Targets gut pathogens and supports microbial balance [97, 101]	Overuse or misuse may disrupt microbial equilibrium [97, 101]
Antimicrobial effects	Rebalances gut dysbiosis with certain SSRIs and TCAs [98, 101]	Prolonged antimicrobial effects can alter gut flora permanently [98, 101]
Long-term medication use	Allows microbial restoration strategies when managed carefully [101, 105]	Unmanaged long-term use may lead to dysbiosis and complications [101, 105]

Table 2. Effects of probiotics, prebiotics, FMT, and dietary interventions

Category	Mechanism	Key Findings
Probiotics	Modulate gut microbiota composition and neurotransmitter levels, reducing inflammation	Improved depressive symptoms in MDD patients [13]; enhanced mood in healthy individuals [106]
Prebiotics	Encourage growth of beneficial bacteria, reduce cortisol levels, and enhance cognitive functions	Reduced cortisol and improved cognitive processing in healthy volunteers [24]
Fecal microbiota transplantation	Reset gut microbiota composition to improve mood and depressive symptoms	Demonstrated antidepressant-like effects in animal models and humans [52]
Dietary interventions	Increase fiber intake and fermented foods, improving gut health and reducing inflammation	Improved mood and decreased depression risk through better microbiota composition [107]

The impact of diet on MGBA and depression

Diet plays a critical role in influencing the MGBA and mental health. Unhealthy dietary patterns, such as high-fat, low-fiber diets typical of the Western diet, disrupt gut microbiota, increase intestinal permeability, and promote inflammation, contributing to depression [107]. Conversely, adherence to healthy dietary patterns, such as the Mediterranean diet rich in fiber, fruits, vegetables, and whole grains, is associated with reduced depression risk [93].

Prebiotics and probiotics also offer therapeutic potential by modulating gut microbiota. Prebiotics promote the growth of beneficial bacteria, reduce stress-induced cortisol, and improve depressive-like behaviors [24]. Probiotics have shown a significant reduction in depressive symptoms, although the best strains, dosages, and duration of treatment require further study [111]. Nutritional strategies, such as omega-3 fatty acid supplementation, also demonstrate antidepressant effects due to their anti-inflammatory properties and role in neurotransmitter function [112]. In both adults and children, omega-3 fatty acids have been shown to support cognitive

Table 3. Dietary patterns and their effects on MGBA and depression

Diet	Characteristics	Effects on gut microbiota	Anti-inflammatory properties	Mental health outcomes
Mediterranean	Rich in fruits, vegetables, whole grains, nuts, olive oil, fish	Increases beneficial bacteria (e.g., *Lactobacillus*, *Bifidobacterium*)	High; reduces systemic inflammation	Reduced risk of depression and improved mood
Western	Processed foods, high in sugar and saturated fats, low in fiber	Reduces microbial diversity; increases pathogenic bacteria	Low; promotes inflammation via high fat/ sugar content	Increased risk of depression, anxiety, and mood swings
Japanese	Rich in fish, soy products, green tea, rice, fermented foods, low in red meat	Enhances gut microbiota diversity; supports beneficial strains	Moderate; linked to lower levels of inflammation	Lower depression risk; enhanced emotional well-being

function by enhancing attention, learning, and working memory. It also supports emotional regulation by reducing mood swings, irritability, and anxiety symptoms. In addition, neuroplasticity is supported by promoting brain connectivity and hippocampal health, which are frequently impaired in depression [113, 114].

Several essential nutrients, including vitamin D, B vitamins, and zinc, are vital for mental health. Deficiencies in these nutrients have been linked to a higher risk of depression, as observed in systematic reviews and meta-analyses [115, 116]. Overall, dietary interventions incorporating these nutrients show promise for depression prevention and treatment, though more research is needed to identify optimal approaches.

Tryptophan's involvement in mood regulation

Tryptophan, an essential amino acid and precursor to serotonin, plays a crucial role in mood regulation [117]. Since the liver stores limited tryptophan, daily intake through foods like dairy, eggs, meat, and fish is necessary to maintain adequate serotonin production. Tryptophan deficiency can increase the risk of depression and is sensitive to factors such as prolonged cooking and artificial sweeteners like aspartame [118, 119].

Studies show that acute tryptophan depletion can significantly reduce serotonin levels, leading to depressive-like symptoms in both rodents and humans [120]. A balanced diet with sufficient tryptophan, carbohydrates for absorption, and other cofactors such as magnesium supports serotonin synthesis and brain function. More research is needed to understand the complex interactions between tryptophan metabolism and mood regulation.

The role of omega-3 fatty acids in depression

Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA), exhibit significant antidepressant effects due to their role in neurotransmitter function, anti-inflammatory properties, and protection of brain cells. Meta-analyses show that EPA supplementation reduces depressive symptoms and may serve as an adjunctive therapy for depression [121, 122].

The brain is supported by omega-3 polyunsaturated fatty acids (PUFAs), primarily eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are also associated with a decreased risk of MDD. While eicosapentaenoic acid (EPA) lowers neuroinflammation, a major contributing factor to depression, DHA promotes neurogenesis and signal transduction. Omega-3s enhance neuroplasticity, emotional control, and cognitive performance [113, 114, 121, 122].

Short-term trials have demonstrated that omega-3 supplementation helps in managing and preventing depression due to its involvement in cognitive and emotional function, particularly through the antidepressant properties of EPA. [123]. While promising, further research is needed to determine optimal dosages, long-term effects, and individual responses. Overall, omega-3 fatty acids hold the potential for treating and preventing depression, warranting further investigation.

Folic acid: fundamental in more than one way

Vitamin B_9 (folate) deficiency is common in individuals with depression, impacting cognitive func-

tion and increasing the risk of depressive symptoms [124]. Elevated homocysteine levels, often linked to low folate, are associated with major depressive disorder [125]. Other micronutrients, such as vitamin B_1 (thiamine), have also been implicated in depression [126].

Research highlights the importance of a nutrient-dense diet in mental health. Diets high in processed and refined foods are associated with increased depression risk, whereas diets rich in fruits, vegetables, whole grains, and lean proteins are linked to improved mental well-being [15]. Addressing deficiencies in folate, thiamine, and other vitamins through diet or supplementation may enhance cognitive function and support mental health.

In summary, diet significantly influences MGBA and mental health. Unhealthy dietary patterns disrupt gut microbiota and promote inflammation, contributing to depression. Conversely, nutritional interventions like the Mediterranean diet, omega-3 supplementation, and micronutrient intake show promise in improving mental health outcomes. Targeting nutrition, probiotics, and prebiotics can enhance the MGBA and serve as an adjunctive strategy for treating and preventing depression. Further research is needed to refine these interventions and fully understand their mechanisms.

Conclusion. The microbiota-gut-brain axis represents a promising target for novel therapeutic strategies in managing major depressive disorder. By elucidating the mechanisms underlying gut-brain interactions, this review highlights the potential of dietary modifications, probiotics, prebiotics, and emerging interventions such as FMT in alleviating depressive symptoms. The integration of microbiota profiling into clinical practice offers the opportunity for personalized treatments, addressing individual variability in gut composition. Furthermore, a deeper understanding of microbial metabolites and their interactions with neural pathways could pave the way for innovative pharmacological therapies.

When combined, these microbiota-targeted therapeutics provide novel avenues for the treatment of depression, especially in those who do not respond to traditional treatments like psychotherapy or antidepressants. Personalized methods that are informed by host genetics, metabolomic data, and microbiota characterization may result in safer, more efficient, and customized treatment plans.

To put these discoveries into clinical practice going forward, multidisciplinary cooperation across psychiatry, neurology, microbiology, and nutritional science is crucial. Large-scale, longitudinal human trials should be the main focus of future research in order to determine efficacy, the best intervention techniques, and long-term results. We are getting closer to a new precision psychiatry paradigm that incorporates the gut microbiota into the foundation of mental health treatment as we learn more about the MGBA and its function in depression.

Future directions should prioritize interdisciplinary research, combining advances in microbiology, neuroscience, and clinical psychiatry to create comprehensive treatment frameworks. As the MGBA's complexities are unraveled, its therapeutic potential can be harnessed to revolutionize mental health care, offering hope for individuals grappling with the challenges of depression.

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ВЕЛИКИЙ ДЕПРЕСИВНИЙ РОЗЛАД І ВІСЬ МІКРОБІОМ-КИШКІВНИК-МОЗОК

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Центральна нервова система та шлунково-кишковий тракт двонаправлено пов'язані через вісь «кишківник-мозок» (GBA). Згідно з гіпотезою мікробіоти кишківника, зміни у складі та активності мікробіоти кишківника можуть впливати на GBA, сприяючи розвитку ментальних захворювань, таких як депресія та відчуття тривоги. Мета цього огляду – проаналізувати, як дисбаланс мікробіоти може впливати на функціонування осі «кишківник-мозок», призводити до змін у метаболізмі, імунній системі та нейротрансмітерах, які асоціюються з депресією. Розглядається вплив змін у харчуванні, потенціал пробіотиків, пребіотиків і симбіотиків для відновлення балансу мікробіоти, а також важливість інтеграції профілювання мікробіоти в персоналізовану клінічну практику.

Ключові слова: вісь мікробіота-кишківник-мозок, депресивні розлади, пробіотики, дієтичні моделі, персоналізоване лікування.

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