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THE ROLE OF GUT MICROBIOTA IN THE PATHOGENESIS OF DEPRESSION - CURRENT STATE OF KNOWLEDGE

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ABSTRACT

In recent years, there has been growing interest in the role of the gut microbiome in modulating brain function and its potential impact on mental disorders, including depression. The gut-brain axis, a complex communication network between the gastrointestinal tract and the central nervous system, is crucial for comprehending the relationship between gut microbiota and mental health. Communication along this pathway takes place through various pathways: neuronal, hormonal, and immunological. Multiple preclinical and clinical investigations demonstrate that alterations in the composition and diversity of gut microbiota can influence neuroinflammatory mechanisms, neurotransmitter metabolism, and hypothalamic-pituitary-adrenal (HPA) axis function, potentially facilitating the emergence of depressive symptoms. This article aims to examine contemporary findings about the mechanisms by which the gut microbiome affects mood and to evaluate potential treatment strategies, including psychobiotics, dietary modifications, and fecal microbiota transplantation. Comprehending the function of the microbiome in the etiology of depression could provide novel avenues for the diagnosis and treatment of affective disorders.Although the current state of knowledge does not yet allow the formulation of concrete conclusions and diagnostic and therapeutic recommendations, it certainly encourages further research.

Materials and methods: A review of the literature available in the PubMed and Google Scholar databases was performed, using the key words: “depression”, “gut microbiota”, “microbiome”, “probiotics”, “prebiotics”, “psychobiotics”.

KEYWORDS

Depression, Gut Microbiota, Microbiome, Probiotics, Prebiotics, Psychobiotics

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1. Introduction

Depression is among the most prevalent mental diseases globally and imposes a considerable burden on individuals and healthcare systems. Notwithstanding considerable advancements in the research of its etiology, the mechanisms underlying this intricate sickness remain inadequately comprehended. Conventional therapy methods, mostly focused on the manipulation of neurotransmitters including serotonin, dopamine, and noradrenaline, fail to yield significant improvement in certain patients[1]. Consequently, there is an increasing interest in alternate pathophysiological mechanisms that may affect the onset and progression of depression.

Over the past two decades, substantial data has emerged indicating a potential association between depression and inflammatory processes. Its presence is closely associated with various somatic diseases and chronic conditions. Numerous parallels exist between the manifestations of depression and the physiological reactions to illness and inflammation[2]. These observations lead to the conclusion that depression may be seen as a psychoneuroimmune disorder in which cytokines are crucial for neurochemical and neuroendocrine functions.

The correlation between immune system activation and depression is further confirmed by the frequent occurrence of depression in the context of inflammatory diseases such as multiple sclerosis, coronary heart disease, HIV, inflammatory bowel disease and rheumatic diseases. An increasing volume of research emphasizes the significance of the gastrointestinal tract, issues with intestinal barrier integrity, and the ensuing activation of the inflammatory response in the onset of various chronic diseases, including inflammatory bowel disease, type 1 diabetes, allergies, asthma, and psychiatric disorders such as autism and depression.

An expanding amount of research indicates connections between this mental disease and the gut microbiome. The disparities in gut microbiota composition between healthy individuals and those afflicted by depression have been substantiated. Research involving animals has consistently demonstrated a correlation between gut microbiota and behavior. The diverse types and strains of bacteria in the gut microbiota influence the body's functions in various manners. The gut microbiota may contribute to the development of depression through mechanisms such as bidirectional communication via the gut-brain axis, production of pro-inflammatory cytokines in response to bacterial lipopolysaccharide, alterations in the concentrations of substances linked to various metabolic pathways, and neurotransmitter-mediated signaling.

This research aims to elucidate the current understanding of the gut microbiome's function in mood regulation and its significance in the etiopathogenesis of depression. Significant focus is directed towards the molecular and physiological mechanisms governing the relationship between the microbiota and the brain, alongside possible therapeutic opportunities arising from the modulation of the gut microbiota.

2. The gut microbiome and its significance in the human body

The gut microbiota is the community of microbes inhabiting the gastrointestinal system, contributing to numerous physiological activities of the body. It is estimated that the human digestive tract is inhabited by over 100 trillion microorganisms, mainly bacteria, but also viruses, archaea and fungi [3]. Intricate and dynamic interactions occur among these gut microbes, which collectively influence the balance of the gut microecology. The large intestine contains the highest concentration of bacteria. The predominant bacterial phyla are *Firmicutes* and *Bacteroidetes*, while *Actinobacteria, Proteobacteria, Verrucomicrobia*, and others are also present.

Many factors can influence the composition and relative abundance of different microorganisms, including genetics, age, geography, lifestyle, drugs, illnesses, immune system and diet. The gut microbiota is dynamic during the human lifespan, with its diversity evolving over time.

Research indicates that diet is the most significant and alterable element affecting the composition of the gut microbiota [4]. A fiber-rich diet fosters the proliferation of advantageous bacteria like *Bifidobacterium* and *Lactobacillus*, resulting in the synthesis of short-chain fatty acids and the enhancement of gut health. A diet rich in saturated fats and simple sugars, while low in fiber, correlates with diminished microbial diversity by decreasing or eradicating beneficial gut bacteria, such as *Alistipes* and *Bacteroides spp*., and concurrently elevating harmful bacteria, including *Faecalibacterium spp*., thereby contributing to dysbiosis and an augmented risk of various diseases[5][6].

Genetic factors of the host also affect the composition of the gut microbiota by modulating the expression of genes associated with the immune system, gut barrier, and metabolism.

The gut microbiome's composition is dramatically affected by the drugs we consume, particularly antibiotics. Antibiotic treatment, particularly with broad-spectrum antibiotics, can diminish the richness of the gut microbiome and facilitate colonization by opportunistic pathogens like *Clostridioides difficile*. Additional

medications, including proton pump inhibitors, metformin, and nonsteroidal anti-inflammatory drugs, also influence the composition of the gut microbiota, however their mechanisms of action are less direct[7].

Elements include physical activity, psychological stress, animal interaction, cleanliness standards, and living environment (urban versus rural) substantially influence microbiota composition. Individuals residing in rural areas demonstrate higher microbial variety compared to urban inhabitants, attributed to their exposure to a broader spectrum of microorganisms. Chronic stress can influence the composition and function of the microbiota via the brain-gut-microbiota axis, hence affecting immune response and metabolism.

The composition of the microbiota undergoes dynamic changes with aging. In neonates, the microbiota is sparse and unstable, predominantly featuring bacteria from the genera *Staphylococcus, Streptococcus, and Enterococcus*, with the manner of delivery significantly influencing the first colonization of the neonatal gut microbiota. Infants delivered vaginally acquire bacterial colonization from the maternal vagina, including *Lactobacillus* and *Bifidobacterium*. Conversely, infants delivered via caesarean section possess a microbiota that closely resembles skin bacteria and the hospital environment, potentially resulting in a delayed colonization of advantageous bacteria, such as *Bacteroides*. Breastfeeding also supports the healthy growth of the microbiota by providing beneficial bacteria and important nutrients that help shape the developing immune system. As individuals develop, the microbiota exhibits increased diversity, characterized by the predominance of bacteria from the genera Bacteroides, *Firmicutes,* and *Lactobacillus.* In advanced age, there is a reduction in microbiota diversity and an elevation in potentially harmful bacteria, which may be significant for the onset of chronic diseasesincluding chronic intestinal inflammation (e.g. Crohn's disease, ulcerative colitis), irritable bowel syndrome (IBS), obesity, type 2 diabetes, and an association between disturbances in the composition of the microbiota and neuropsychiatric disorders such as depression has also been observed[8].

The human gut microbiota is essential for sustaining homeostasis. Its functions encompass many physiological, immunological, and metabolic processes vital for human health.The gut microbiota participates in the digestion and fermentation of nutrients, including sugars that are indigestible by humans. Fermentation generates short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, which serve as vital energy sources for intestinal epithelial cells and influence hepatic metabolism and the immune system[9]. Specifically, butyrate serves as a principal energy substrate for colonic epithelial cells[10].The microbiome also contributes to the manufacture of vitamins (e.g., K, B12, B9), bile metabolism, and the transformation of medicines and xenobiotics [11].The gut microbiome significantly influences and regulates the immune response. The interactions between bacteria and immune cells, including intestinal epithelial cells, macrophages, dendritic cells, and T and B lymphocytes, are essential for preserving immunological homeostasis. Dysbiosis, characterized by an imbalance in the microbiota, may result in persistent inflammation and heightened vulnerability to inflammatory bowel disease and other immunological illnesses[12].The gut microbiota serves as a protective barrier against harmful microbes by fighting for resources and synthesizing antibacterial compounds. Moreover, gut microbes enhance the synthesis of secretory immunoglobulin A (sIgA), which is crucial for infection defense[13].

The gut microbiota affects central nervous system function by producing neuroactive metabolites (such as GABA, serotonin, and dopamine), modulating the hypothalamic-pituitary-adrenal (HPA) axis, and interacting with the vagus nerve. Alterations in the microbiome been noted in individuals with depression, irritable bowel syndrome, Parkinson's disease, and autism spectrum disorder[14][15].

3. Mechanisms of the Gut–Brain Axis and Their Relevance in the Pathogenesis of Depression

The gut-brain axis (GBA) is a mechanism that integrates signals between the gastrointestinal tract and the central nervous system (CNS). This axis is a multifaceted, dynamic communication system facilitating bidirectional information flow among the neurological system, immunological system, endocrine system, and gut bacteria. GBA is crucial for maintaining organismal homeostasis, contributing to the regulation of metabolic and immunological processes, as well as the modulation of cognitive and emotional activities.

The GBA predominantly pertains to the central nervous system, specifically focusing on limbic regions, the hypothalamus, and the brainstem, which are crucial to the processing of autonomic and emotional information. Communication with the gastrointestinal tract occurs via the autonomic nervous system, primarily the vagus nerve, and the enteric nervous system (ENS), which is a local neural network capable of autonomously regulating motor and secretory functions of the intestines.The hypothalamic-pituitary-adrenal (HPA) axis is a principal mechanism of systemic control, essential for the stress response. Neuronal and humoral signals from the gut can modulate the functioning of this axis by altering cortisol and other stress hormone levels, which subsequently reciprocally affects the microbiota and gastrointestinal function.The

intestines constitute the most extensive immunological organ in humans. Their mucosa harbors a substantial quantity of immune cells situated within GALT (gut-associated lymphoid tissue) structures. The integrity of the intestinal barrier and immunological equilibrium is essential in preventing inflammation, the chronic stimulation of which can profoundly affect brain function[16].Proinflammatory cytokines and other inflammatory mediators can traverse the blood-brain barrier or influence its permeability, resulting in microglial activation and neuroinflammatory alterations in the central nervous system.The microbiota residing in the gastrointestinal system is a crucial component of the gut-brain axis (GBA). It affects various biological functions via the synthesis of metabolites, neurotransmitters, and the control of the immunological and neurological systems.The microbiota residing in the gastrointestinal system is a crucial component of the gut-brain axis (GBA). It affects various biological functions via the synthesis of metabolites, neurotransmitters, and the control of the immunological and neurological systems.

Research suggests that alterations in the composition and diversity of the microbiota, termed dysbiosis, may be associated with depressed symptoms[17].The impact of gut microbiota on depression may transpire through many routes. Gut microbes can synthesize and modulate neurotransmitters, including serotonin, dopamine, gamma-aminobutyric acid (GABA), and norepinephrine, which are crucial in the pathophysiology of depressive disorders.The metabolism of tryptophan, an amino acid that serves as a precursor to serotonin, is of particular significance. Disruptions in the microbiota can divert tryptophan to the kynurenine pathway, resulting in elevated synthesis of neurotoxic metabolites (e.g., quinolinic acid) and reduced serotonin levels.

Intestinal dysbiosis may induce heightened activation of the HPA axis, resulting in increased cortisol levels—a stress hormone—whose prolonged presence might facilitate the onset of depression. Depression is frequently associated with increased concentrations of proinflammatory cytokines (e.g., IL-6, TNF-α, IL-1β). Intestinal dysbiosis can result in heightened intestinal barrier permeability ("leaky gut"), facilitating the translocation of lipopolysaccharide (LPS) and the activation of the inflammatory response[18]. Chronic immunological activation enhances neuroinflammation and alters neurotransmission, potentially worsening depression symptoms.Bacterial fermentation products, specifically short-chain fatty acids (SCFA) – predominantly butyrate, propionate, and acetate – exhibit anti-inflammatory properties, enhance the intestinal barrier, and influence enteric neurons and glial cells. Butyrate possesses neuroprotective properties and influences gene expression via inhibiting histone deacetylases (HDACs), which may be crucial for neuroplasticity.

Comprehending the mechanisms governing microbiota–brain–immune system interactions unveils novel therapeutic and preventative opportunities, particularly in psychiatric conditions like depression.

4. Interactions Between the Gut Microbiome and the Nervous System in Relation to Depression

An increasing body of scientific evidence indicates a significant association between alterations in the composition of the gut bacterial microbiota (dysbiosis) and the occurrence of major depressive disorder (MDD). The most consistently observed pattern involves an increase in pro-inflammatory bacteria alongside a reduction in anti-inflammatory microbial populations.In individuals with MDD, disturbances have been most frequently reported among three dominant bacterial phyla: *Firmicutes, Actinobacteria*, and *Bacteroidetes*. Notably, an elevated *Bacteroidetes*-to-*Firmicutes* ratio is often observed, characterized by an increased abundance of *Bacteroides* and a decreased presence of *Blautia, Faecalibacterium*, and *Coprococcus*[19]. In addition, numerous studies have documented elevated levels of *Eggerthella* and reduced abundance of *Sutterella* in patients diagnosed with depression[19].

In dysbiosis, the gut-brain axis function is disrupted, leading to enhanced neuroinflammatory processes and compromised blood-brain barrier integrity. Changes in the structure and function of the gut microbiota may influence depressive symptomatology through several mechanisms, including modulation of neurotransmitter synthesis and release (e.g., serotonin and dopamine), stress response regulation, and altered function of the hypothalamic–pituitary–adrenal (HPA) axis. These disturbances can also lead to altered expression of neurotrophic factors such as BDNF and increased production of pro-inflammatory cytokines. Patients with depression often exhibit elevated levels of C-reactive protein (CRP) and interleukins such as IL-1, IL-2, IL-6, IFN-γ, and IL-1β[20].

In one study, *Mycobacterium neoaurum* was isolated from the feces of men with MDD. This strain is capable of degrading testosterone via the expression of 3β-hydroxysteroid dehydrogenase (3β-HSD). Experimental oral administration of this bacterium to rats induced depressive-like behaviors[19].

In the case of irritable bowel syndrome (IBS)—a disorder associated with immune dysfunction—a correlation was found between gut microbiota composition and the volume of specific brain structures in IBS patients with a history of early-life trauma. These individuals exhibited a shift in the *Firmicutes*-to-

Bacteroidetes ratio, marked by *Firmicutes* dominance and a decrease in *Bacteroidetes*. Interestingly, no significant association was found between these microbial shifts and the severity of depressive or anxiety symptoms. A contrasting pattern was observed in individuals with depression but without IBS, where the *Firmicutes/Bacteroidetes* ratio was reversed[21].

The gut microbiota plays a key role in modulating brain function through the production of neuroactive compounds. Certain bacterial strains produce molecules identical to neurotransmitters found in the nervous system, such as GABA, dopamine, acetylcholine, serotonin, and norepinephrine. Importantly, these same molecules also exhibit immunomodulatory functions, thereby influencing immune system activity[22]. Short-chain fatty acids (SCFAs), particularly butyrate, possess strong anti-inflammatory properties and support the integrity of the intestinal barrier. SCFAs also stimulate enterochromaffin cells to release serotonin, which not only acts locally in the gut but may also influence the vagus nerve and systemic circulation[22].

An intriguing discovery is the transmissibility of depressive symptoms through fecal microbiota transplantation (FMT). Mice that received microbiota from depressed patients exhibited more pronounced depressive-like behavior compared to those that received microbiota from healthy donors. Similar findings were obtained when microbiota from depressed individuals was transferred to microbiota-depleted rats, which subsequently displayed increased anxiety-like behaviors, anhedonia, and disrupted tryptophan metabolism. No such alterations were observed in animals receiving microbiota from healthy controls, pointing toward a causal role of gut microbiota in the development of depressive symptoms[23].A comprehensive analysis of fecal microbiota transplantation reports will be included later in this document.

In summary, the composition and abundance of the gut microbiota in individuals and animals with depression show distinct differences compared to healthy controls. At the family taxonomic level, certain microbes—such as *Paraprevotella*—have been positively associated with depressive symptoms, whereas others, including *Streptococcaceae* and *Gemella*, show an inverse relationship. Among bacterial genera, elevated levels of *Prevotella, Klebsiella*, and *Clostridium* have been linked to increased symptom severity. Dysbiosis may significantly contribute to depression through its effects on protein expression within tissues involved in the gut–brain axis[24].

5. Therapeutic Potential of Gut Microbiome Modulation in the Context of Depression

5.1. Probiotics, prebiotics and psychobiotics

The definition of a probiotic has evolved over the years since its original version formulated by Lilly and Stillwell in 1965, which referred to a substance influencing the balance of the microbiota. In 1991, Fuller further developed this concept, describing a probiotic as a mixture of bacterial cultures or single microorganisms that have a beneficial effect on the improvement of the gut microflora after being administered to the host. The current definition provided by the WHO is:"Probiotics are microorganisms which, when administered in adequate amounts, confer a health benefit on the host"[25].

The purpose of their use is to modify the gut microbiota in such a way that it promotes the growth and colonization of beneficial probiotic bacteria and minimizes the development of harmful microorganisms. Probiotics play a role in breaking down and eliminating unnecessary metabolic by products, such as uric acid. A desired probiotic should also exhibit antibiotic resistance and support the integrity of the intestinal mucosal barrier by stimulating the synthesis of mucins and tight junction proteins.Ideally, the microorganisms should be of human origin and encapsulated in microcapsule form to ensure prolonged and enhanced clinical efficacy. However, care must be taken to prevent their degradation during industrial processing or metabolic transformations in the gastrointestinal tract before they reach the colon. Currently, probiotics are formulated in a way that protects them from destruction by stomach enzymes or acidic pH. Additionally, their ability to adhere to epithelial cells facilitates their replication and colonization in the intestines.Probiotics may be supplied in the form of naturally occurring microorganisms found in foods (such as fermented products or fresh vegetables) or in ready-made dietary supplements containing selected beneficial strains[26][27].

In order for probiotics to effectively grow and proliferate in the large intestine during personalized therapy, they should be administered together with prebiotics, which serve as their nutritional source. A prebiotic is a substrate specifically used by host bacteria that provides a health advantage. Prebiotics are generally indigestible food elementsthat promote the proliferation and function of advantageous gut bacteria, including *Bifidobacterium* and *Lactobacillus.* Prebiotics comprise compounds such as inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), and resistant starch.Therefore, the synergistic combination and co-administration of both substances- probiotics and probiotics- is essential for enhancing

therapeutic efficacy particularly in patients already diagnosed with gut dysbiosis, which impairs the colonization of new bacteria[27].

The term psychobiotic was introduced in 2013. This pertains to bacteria (probiotics) or compounds that enhance their efficacy (e.g., prebiotics) which influence the central nervous system by modifying intestinal microbiota, leading to increased mood, diminished anxiety, alleviated depression symptoms, or enhanced cognitive functioning.Main groups of psychobiotic bacteria that positively affect the gut–brain axis and help alleviate symptoms of depression, anxiety, or chronic fatigueare presented in Table 1.

Table 1. Main groups of psychobiotic bacteria

Psychobiotic bacteria	
Lactic acid bacteria – *Lactobacillus*	**Bacteria of the genus – *Bifidobacterium***
The most numerous group of probiotic bacteria that synthesize butyric acid, contributing to a decrease in intestinal pH, which in turn reduces the number of harmful microorganisms in the large intestine.	Primarily contribute to the production of B-group vitamins and the breakdown of dietary fiber.
Lactobacillus helveticus, Lactobacillus reuterimLactobacillus acidophilu, Lactobacillus rhamnosus, Lactiplantibacillus plantarum	*Bifidobacteriumlongum, Bifidobacteriuminfantis*

5.2. Selected Bacterial Strains with Antidepressant Effects

Disruption of the microbiota–gut–brain axis in depressive disorders indicates a link between emotional disturbances and changes in the composition of the gut microbiota. Evidence suggests that the condition of our intestines has a profound impact on brain function by influencing neurotransmitters and their precursors dopamine, serotonin, and GABA in the central nervous system. In particular, dysbiosis of the microbiome may contribute to the later onset of depressive symptoms.

The use of specific strains of probiotic bacteria, referred to as psychobiotics, has shown stress-relieving effects through modulation of the gut microbiota, thereby enhancing the immune function of the intestinal mucosa and the systemic immune response. The most extensively studied bacterial genus in depression treatment is *Lactobacillus*, as its increased presence in the colon contributes to the alleviation of anxiety and stress symptoms.A study conducted by Zhu et al. [28]included three groups of students undergoing an exam session. In this experiment, one group was administered a probiotic while simultaneously being exposed to stress; the second group was exposed to stress without probiotic supplementation; and the third group consisted of individuals not participating in the exam session (control group). The aim of the study was to demonstrate that the administration of the JYLP-326 probiotic (*Lactobacillus plantarum* strain) improves gut microbiota diversity and alleviates stress, illustrating the protective effects of the probiotic. The group exposed to stress and given the probiotic exhibited a gut microbiota profile similar to the non-stressed control group. However, stress altered the gut microbiota to such an extent that even the administration of the JYLP-326 probiotic could not restore the original microbiome composition. This demonstrates that even a probiotic cannot fully restore the baseline intestinal microbiota.

Another important study confirmed the positive effects of *Lactobacillus* and *Bifidobacterium* strains on the gut microbiome, with the addition of an antidepressant -fluoxetine. The experiment was conducted on mice subjected to chronic unpredictable mild stress (CUMS). In these animals, an increase in serotonin levels, a significant improvement in mood, and a reduction in proinflammatory cytokines were observed. The addition of fluoxetine to the probiotic demonstrated a synergistic effect, resulting in enhanced therapeutic outcomes in the treatment of CUMS[29].

In another study conducted by Tillmann S. et al., it was observed that administration of *Bifidobacterium longum* and *Lactobacillus helveticus* to rats increased hepatic levels of S-adenosylmethionine (SAM) a compound involved in the synthesis of neurotransmitters such as serotonin. These strains also reduced dopamine concentrations in plasma, since chronic stress leads to excessive dopamine secretion into the bloodstream and insufficient levels in the brain, which exacerbates depressive disorders[30].

5.3. The Importance of Prebiotics and a Fiber-Rich Diet

Our diet has a profound impact on the composition of our gut microbiota; therefore, poor dietary habits or obesity lead to its disruption, contributing to general malaise. When consuming food, we aim not only to obtain valuable nutrients but also to derive health benefits. People seeking to improve the composition of gut microorganisms look for so called "beneficial bacteria" primarily in natural products, particularly in the form of soluble fibers found in raw vegetables and in carbohydrates selectively fermented by gut microbes. A key group of such foods includes products obtained through fermentation, including dairy, cereal, meat, and vegetable-based items[26]. Fermented foods influence specific groups of microorganisms, allowing for the modification of their abundance and diversity[31].Furthermore, a proper diet should also be rich in prebiotics, vitamins, and minerals[26].

Prebiotics exert a positive influence on the gut microbiome and consequently on the entire organism through substances that are selectively metabolized by microbes within the microbiota. They provide nutrients for bacteria in the colon to stimulate their growth. Prebiotics derived from oats or soy (e.g., cellulose) should also demonstrate resistance to stomach acid in order to support the gut microbiome in the large intestine. Substances such as fiber and resistant starch (highly resistant to digestion) are fermented only in the colon, as they are not absorbed in the small intestine. This process leads to the proliferation of beneficial microorganisms, which supports mental health[32].

The primary prebiotics used (many of which also serve as dietary fibers) to enhance psychological well-being include inulin derivatives, GOS (galactooligosaccharides), and FOS (fructooligosaccharides).Here areinstances of prebiotics:

- Fructans (FOS and inulin) are water-soluble plant-derived compounds composed of multiple fructose units. Inulin, for example, which has a β-configuration at the anomeric C2 position, is not digested but undergoes fermentation only in the colon. These compounds are found in significant amounts in wheat, rye, onions, bananas, and asparagus. The polyphenols present in these foods help reduce intestinal inflammation.
- Galactooligosaccharides (GOS) are composed of several galactose molecules terminated with a glucose molecule, forming lactose derivatives that are indigestible. Found in dairy products and cereals, they support the growth of beneficial *Bifidobacterium* and *Lactobacillus* strains. Moreover, they inhibit the adhesion of pathogens to the intestinal epithelial cells by mimicking cellular receptors, which helps reduce the synthesis of harmful substances and restores the balance between microbial strains in the colon.
- Resistant starch, through fermentation in the colon, produces butyric acid, which helps alleviate inflammation in the intestines. It is found in leguminous vegetables.
- Polyphenols have both anti-inflammatory and antioxidant properties.

5.4. Fecal Microbiota Transplantation (FMT) and Depressive Disorders

Fecal microbiota transplantation (FMT), administered in the form of a fecal suspension to a recipient, aims to restore a healthy bacterial environment by increasing microbial diversity and displacing harmful pathogens from the colonic ecosystem.

The introduction of processed fecal material from a donor is typically carried out via enemas, endoscopy (using a nasojejunal tube), colonoscopy, or oral capsules. FMT is commonly used in recurrent *Clostridioides difficile* infections, irritable bowel syndrome (IBS), and small intestinal bacterial overgrowth (SIBO). However, it may also be considered in individuals suffering from symptoms such as depression, anxiety, and chronic stress. Fecalsamples from individuals with these symptoms often show a reduced abundance of *Ruminococcaceae*, *Lachnospiraceae*, *Lactobacillus*, and *Bifidobacterium* strains[33][34].

To ensure safety during FMT, strict criteria for selecting healthy donors are followed to prevent the transmission of serious and unnecessary diseases to the recipient. The procedure includes a detailed interview with the potential donor and screening tests, such as serological assays for syphilis, hepatitis, HIV, and microbiological stool examinations for parasites, among others. The exact criteria may vary depending on the institution performing the procedure. Nevertheless, the long-term effects of FMT remain unknown, as current screening methods cannot exclude future emergence of as yet undetected diseases or responsible microorganisms.

Despite justified concerns regarding fecal transplantation, the use of bacteria from universal stool donors is desirable, as these institutions maintain comprehensive medical histories of donors and can continuously monitor and modify their collected microbiota, as well as detect potential future risks. Utilizing databases of universal stool donors allows for omission of the donor-screening process and reduces treatment costs. One limitation, however, is the lack of understanding of the mechanisms underlying the interactions between introduced microorganisms and existing pathogens in relation to depression. Further studies are also needed

to explore the interplay between genetic factors and the recipient's gut microbiota in response to beneficial bacteria transplanted during FMT[35].

One study conducted by Hu et al. demonstrated that the gut microbiome in rats receiving transplants from healthy donors improved significantly, leading to reduced symptoms of depression and anxiety, better neurotransmission in the brain, and decreased levels of pro-inflammatory cytokines. In this experiment, a group of diseased "Fawn-Hooded" rats received microbiota from healthy "Sprague-Dawley" rats, resulting in improved mood following FMT[34].

Another experiment involved transplanting microbiota into mice whose gut flora had been depleted by antibiotic treatment. These mice were then inoculated with microbiota from donor mice subjected to chronic unpredictable mild stress (CUMS). The recipient mice developed symptoms characteristic of anxiety and depression, as a consequence of the FMT. In conclusion, the transfer of a dysfunctional microbiome between individuals can induce depressive disorders. This occurs via a reduction in beneficial *Lactobacillus* species and an increase in pro-inflammatory bacteria, leading to elevated inflammatory cytokines and reduced levels of neurotransmitters in the brain[33].

Transplanting bacteria from the gut microbiome or using prepared probiotic formulations offers potential for modulating the composition of the gut flora in improving the health of individuals with anxiety-depressive disorders. FMT may even prove more effective than probiotic supplementation, as its effects may be longer-lasting or more robust compared to oral probiotics.It is important to acknowledge that there are no extensive, randomized clinical trials validating the efficacy and safety of FMT in psychiatry.

6. The connections between gut microbiota and antidepressants

An increasing amount of studies indicates that the effectiveness and characteristics of antidepressants may be somewhat influenced by the gut bacteria. Simultaneously, antidepressants influence the composition and function of the microbiome, indicating a bidirectional connection of possible therapeutic significance.

Medications, especially those taken orally, have a significant impact on the composition and function of the gut microbiome.Research indicates that antidepressants can influence antibacterial properties by altering the composition and functionality of the gut microbiome, particularly on Gram-positive bacteria[36]. Prolonged administration of selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCA), and other antidepressants may alter the ratios of commensal and possibly pathogenic bacteria, thereby impacting the equilibrium of the intestinal microbiome[37][38][39].

Vich Vila et al. indicated that the utilization of SSRIs augmented the prevalence of *Eubacterium ramulus* in the gastrointestinal tract, whereas tricyclic antidepressants elevated the abundance of *Clostridium leptum*[40]. Klunemann et al. discovered that duloxetine administration augmented the prevalence of *Eubacterium rectale* by over 100-fold relative to the untreated cohort[41]. The increased number of these bacteria, known for producing butyrate with anti-inflammatory properties, may enhance the therapeutic effects of the medicine, hence augmenting antidepressant treatment[42]. The observations indicate that antidepressants modify the makeup and function of the gut microbiota, potentially elucidating a portion of their antidepressant effects. A recent prospective cohort study by Lee et al. demonstrated that gut microbiota can serve as a predictor of antidepressant treatment outcomes in geriatric depression[43]. The baseline enrichment of flora with *Faecalibacterium, Roseburia*, and *Agathobacter* in comparison to *Lachnoclostridium* (reference system) was correlated with alleviation of depression.

Certain antidepressants can influence the synthesis of short-chain fatty acids (SCFAs), neurotransmitters, and proinflammatory cytokines, hence indirectly impacting the operation of the gut-brain axis [44]. Alterations in the microbiota may significantly influence not only therapy efficacy but also the emergence of undesirable consequences, such gastrointestinal illnesses.

The gut microbiota can affect the metabolism of antidepressants both directly, via enzymatic conversion of active compounds, and indirectly, by modulating the expression of transport proteins and host enzymes.Certain gut bacteria has the capability to biotransform antidepressants, particularly tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs)[41]. Organisms like *Eggerthellalenta* and *Clostridium spp*. possess enzymes that can reduce aromatic rings, facilitate deamination, and execute other chemical events that result in the inactivation of pharmaceutical compounds or alterations in their pharmacological characteristics. Drug bioaccumulation, a process whereby bacteria assimilate drug molecules without chemical alteration, may also result in diminished bioavailability.

The microbiota affects metabolic pathways essential for the efficacy of antidepressants, specifically the metabolism of tryptophan, an amino acid that serves as a precursor to serotonin. Dysbiosis may enhance the

kynurenine pathway while diminishing the serotonin pathway, leading to decreased serotonin availability and heightened synthesis of neurotoxic metabolites, including quinolinic acid. This disruption of neurochemical equilibrium may diminish the efficacy of SSRIs, which depend on enhancing serotonin availability in the synaptic cleft.

Research indicates that microbiome makeup may predict the efficacy of antidepressant therapy[45]. Responders exhibit an elevated prevalence of specific bacterial taxa, including *Ruminococcaceae*, *Faecalibacteriumprausnitzii*, and *Coprococcus*, which synthesize butyrate known for its anti-inflammatory and neuroprotective properties. Conversely, refractory patients are more inclined to exhibit a prevalence of pro-inflammatory bacteria from the *Proteobacteria* or *Eggerthellaceae* families.

Comprehending the connections between microbiota and antidepressant medication unveils novel therapeutic opportunities, including the advancement of personalized treatment. The microbiome profile may function as a biomarker for treatment response and as a target for supplementary therapies, like psychobiotics or dietary changes. Initial research indicates that augmenting antidepressant therapy with microbiota-modulating therapies may enhance efficacy and mitigate unwanted effects; nevertheless, additional high-quality clinical trials are required.

7. Conclusions

Current studies indicate that the gut microbiota is a significant component of the regulatory system influencing the central nervous system's functionality and, consequently, human mental health. Multiple experimental and observational studies suggest that alterations in the composition and function of the gut microbiota may play a role in the emergence of depressive symptoms via intricate mechanisms, including activation of the hypothalamic-pituitary-adrenal axis, modulation of the immune response, and the synthesis of neuroactive metabolites.

Gut dysbiosis can result in compromised gut barrier integrity, persistent inflammation, and modified neurotransmission, all of which contribute to the pathophysiology of depression. Simultaneously, clinical observations validate the correlation between microbiota profiles and the intensity of depressive symptoms, while also suggesting the potential of microbiological interventions (such as psychobiotics, dietary modifications, or microbiota transplants) as adjuncts to conventional pharmacological and psychotherapeutic treatments.

Nonetheless, despite the accumulating evidence, numerous unresolved questions persist. There is an absence of definitive standards about the makeup of the "optimal" microbiome in psychiatry, along with a scarcity of high-quality clinical trials validating the effectiveness of specific microbiological therapies for treating depression. Additional translational research and personalized medicine strategies are essential to elucidate the connection between the microbiome and depression, and to convert this understanding into effective diagnostic and treatment instruments.

The findings from current investigations underscore the necessity for a comprehensive approach to depression treatment, wherein gut flora plays a crucial role in systemic mood regulation. The amalgamation of microbiology, neurobiology, and psychiatry presents novel prospects for the formulation of more efficacious and personalized therapeutic approaches.

Disclosure

Author's contribution: Patrycja Jędrzejewska-Rzezak; Conceptualisation: Agnieszka Kasprzak; Methodology: Katarzyna Oświeczyńska; Software: Agnieszka Zaleszczyk; Check: Patrycja Jędrzejewska-Rzezak, Katarzyna Oświeczyńska; Formal: Katarzyna Oświeczyńska; Investigation: Agnieszka Zaleszczyk, Agnieszka Kasprzak; Resources: Agnieszka Zaleszczyk, Patrycja Jędrzejewska-Rzezak; Datacuration: Patrycja Jędrzejewska-Rzezak, Katarzyna Oświeczyńska; Writing-Rough Preparation: Agnieszka Kasprzak Agnieszka Zaleszczyk; Writing-Review and Editing: Patrycja Jędrzejewska-Rzezak, Katarzyna Oświeczyńska; Visualisation: Agnieszka Zaleszczyk; Supervision: Agnieszka Kasprzak; Project Administration: Agnieszka Kasprzak.

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