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Gut Microbiota and Mental Health: A Review of the Impact of Gut Bacteria on Depression and Anxiety Disorders

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ABSTRACT

The gut microbiota plays a crucial role in human health, including mental health. Depression and anxiety disorders are among the most common mental illnesses in the population. This review examines recent PubMed literature to evaluate the microbiota's impact on these conditions and potential therapeutic strategies. Gut microbiota affects depression and anxiety through neural, endocrine, and immune-inflammatory mechanisms, involving factors such as BDNF, elevated cortisol during dysbiosis, bacterial endotoxins, and cytokines. Conditions like leaky gut syndrome and SIBO are linked to the development of depression, anxiety, and other disorders, such as autism. Probiotics and prebiotics may alleviate depression by enhancing neuroplasticity, though this effect is better established in animal studies. For anxiety disorders, most studies report unfavorable alterations in gut microbiota composition among affected patients, while a few suggest a beneficial effect of probiotics. Probiotics also reduce side effects of antipsychotic drugs. Antibiotic use has been associated with increased risks of these mental conditions. Attempts have been made to use microbiota transfer therapy (MTT) as a complementary treatment, showing improvements particularly in depression and, to a lesser extent, anxiety, especially among patients recovering from COVID-19, those with irritable bowel syndrome (IBS), and individuals with severe depression. In recent years, numerous

studies have explored the impact of gut microbiota on mental health, highlighting its significant therapeutic potential as an adjunct in treating anxiety and depression. However, there remains a need for more well-designed, large-scale human studies to confirm these findings conclusively.

KEYWORDS: Gut Microbiota; Depression; Anxiety Disorders; Microbiota Transfer Therapy; Mental Health

1. INTRODUCTION

1.1 BACKGROUND ON GUT MICROBIOTA

The gut microbiota, also referred to as the microflora or microbiome, encompasses the diverse community of microorganisms that reside in the human intestines. This intricate ecosystem is predominantly composed of bacteria, although other organisms such as fungi are also present. For a long time, the role of the gut microbiota was underestimated; however, modern research and scientific breakthroughs have highlighted its profound influence on human health. The gut microbiota is now recognized as a critical component in maintaining homeostasis and regulating numerous physiological processes essential for overall well-being. In recent years, the study of gut microbiota has gained remarkable attention. It has been revealed that the state of the microbiota can influence various seemingly unrelated aspects of health, including immune function, metabolism, and even mental health. One particularly fascinating aspect of gut microbiota is its highly individualized nature. Its composition varies significantly among individuals, shaped by genetic predispositions as well as external factors such as lifestyle and environmental exposure. Additionally, notable differences in gut microbiota composition have been observed between populations from different regions of the world. The sheer number of microorganisms in the human digestive tract is astonishing, with estimates suggesting that the adult gut hosts approximately 100 trillion microorganisms, collectively weighing about 1–2 kilograms[1]. This incredible microbial diversity plays a fundamental role in sustaining health. The development of the gut microbiota begins at birth and continues throughout the first few years of life. During this time, exposure to environmental microorganisms helps establish a unique microbiome profile for each individual. A balanced state of gut microbiota is known as eubiosis, while disruptions in its composition or abundance are referred to as dysbiosis. Dysbiosis can have far-reaching health implications, as an imbalanced microbiota may impair immune function and reduce the body’s ability to combat infections, inflammation, or chronic

diseases. It can also lead to a decline in beneficial bacteria and an overgrowth of pathogenic microorganisms. These imbalances are associated with various health issues, including constipation, bloating, allergies, and even mood disorders such as depression.

1.2 OVERVIEW OF MENTAL HEALTH DISORDERS (DEPRESSION AND ANXIETY)

Depression, also known as depressive disorder, is one of the most prevalent mental health conditions and is classified as a mood disorder. According to the DSM-5, depression is characterized by a sustained low mood lasting at least two weeks, accompanied by alterations in affect, cognitive processes, and neurovegetative functions. These symptoms cause significant impairment in the patient's daily functioning. To diagnose a depressive episode, additional criteria must be met, which define the specific symptoms and their severity. A critical aspect of the diagnostic process is conducting a thorough differential diagnosis to distinguish between the natural experience of grief or mourning and a clinical depressive episode. It is important to note that a depressive episode can be diagnosed during its first occurrence; however, depression is recurrent for the majority of patients. Special attention should be given to cases where no remission occurs between episodes, or where low mood persists for over two years in adults (or one year in children). These features may indicate persistent depressive disorder, also known as dysthymia[2].

Anxiety disorders represent a broad and diverse group of mental health conditions characterized by excessive and often disproportionate fear or anxiety. Unlike normal anxiety, which is a typical response to stressful situations, anxiety disorders are marked by chronic and intense anxiety that significantly disrupts the individual's ability to function daily. These disorders are frequently associated with avoidance behaviors, where patients actively try to evade situations, people, or stimuli that provoke anxiety. This category encompasses various clinical entities, including specific phobias, social anxiety disorder, panic disorder, generalized anxiety disorder (GAD), agoraphobia, separation anxiety disorder, and selective mutism. While each of these disorders has its own distinct features, they share a common thread: inappropriate and debilitating anxiety that hinders daily life. This often leads to profound difficulties in social,

professional, and personal domains, highlighting the importance of accurate diagnosis and treatment.

1.3 THE GUT-BRAIN AXIS: A BIDIRECTIONAL COMMUNICATION SYSTEM

The gut-brain axis is a complex network of interactions between the gastrointestinal tract and the central nervous system. This system is heavily influenced by the intestinal microbiota, the biologically active substances it produces, neurohormones, and impulses transmitted via the autonomic nervous system[3]. A defining feature of the gut-brain axis is its bidirectionality—signals flow both from the gut to the brain and from the brain to the gut. However, the term "gut-brain axis" simplifies what is, in reality, a far more intricate system. This axis encompasses several interconnected components, including the neuroendocrine system, the neuroimmune system, the enteric nervous system, the hypothalamic-pituitary-adrenal (HPA) axis, and the vagus nerve. Each of these elements plays a critical role in maintaining the body's homeostasis. For instance, the HPA axis is essential for processing stress stimuli and regulating their effects on various bodily systems[4]. The development of the gut-brain axis begins at birth[5]. A pivotal stage in this process is the colonization of the gastrointestinal tract by microbiota, which profoundly influences the development and functioning of both the digestive and nervous systems. Research suggests that proper maturation of this axis has far-reaching consequences, shaping an individual's physical and mental health across their lifespan. Understanding the mechanisms underlying the gut-brain axis provides promising opportunities in medicine, particularly in the treatment of mental health disorders, gastrointestinal diseases, and metabolic conditions. An increasing body of evidence highlights the significance of dietary and lifestyle interventions in optimizing the functions of this complex system.

1.4 OBJECTIVES AND SCOPE OF THE REVIEW

The medical community increasingly embraces the adage, *"It is better to prevent diseases than to cure them."* A key area that aligns with this philosophy is the rapidly advancing understanding of the gut microbiota and its profound impact on the human body. Numerous studies highlight that the gut microbiota influences a wide range of physiological processes and organ functions. Importantly, its condition can be modulated indirectly through lifestyle modifications, dietary changes, or the use of probiotics, offering new opportunities for

preventing and treating various diseases, including mental health disorders such as depression and anxiety.

This review aims to analyze the existing scientific research on the relationship between the gut microbiota and mental health, with a particular focus on depression and anxiety disorders. It seeks to consolidate comprehensive medical knowledge in one place, providing a valuable resource for researchers interested in this topic. The analysis encompasses the mechanisms of action of the gut microbiota, its potential therapeutic applications, and strategies to modify its composition to support mental health.

In recent years, mental health hygiene has become a prominent topic of public discourse. The modern lifestyle—characterized by stress, haste, and unhealthy dietary habits—has been shown to contribute to the onset or exacerbation of mental health disorders. In this context, the role of the gut microbiota is especially significant, as its regulation could complement traditional therapeutic approaches. This review not only summarizes current knowledge but also identifies gaps in research that warrant further investigation to develop effective, microbiota-centered strategies for mental health support.

The studies analyzed in this review are sourced from PubMed, a highly regarded scientific database, ensuring the quality and reliability of the materials presented.

In conclusion, exploring the gut microbiota's impact on mental health has the potential to deepen our understanding of disease mechanisms and pave the way for innovative, holistic approaches to mental health care. By integrating insights into the gut microbiota with existing therapeutic methods, the medical field can move toward more effective strategies for prevention and treatment.

2. THE GUT MICROBIOTA: COMPOSITION AND FUNCTIONS

The development of the human microbiome is a complex and dynamic process influenced by various factors. A critical moment in this development occurs during delivery, when the newborn is first colonized by symbiotic gastrointestinal microorganisms. However, growing evidence suggests that this process may begin *in utero*, facilitated by vertical transmission through the placenta, amniotic fluid, and meconium[5]. This perspective highlights the direct connection between the health and microbiota of the mother and the initial microbiome of the child, which will undergo further modifications due to environmental influences throughout life.

Evidence for the impact of the intrauterine environment on the fetal microbiome includes findings that children born to mothers experiencing severe stress during pregnancy have reduced levels of Bifidobacterium bacteria[5]. After birth, the mode of delivery plays a significant role in shaping the infant's microbiome. Vaginally delivered infants exhibit greater microbial diversity and abundance compared to those delivered via cesarean section[6]. Feeding practices are equally critical. Breastfeeding, as opposed to formula feeding, supports the favorable development of the microbiota, promoting both a richer composition and greater diversity[3]. As the infant transitions to a more varied diet and grows, the microbiome undergoes further changes. By adulthood, it becomes dominated by two main bacterial phyla: Bacteroidetes and Firmicutes. In contrast, the microbiota of children is characterized by the dominance of Lactobacillus and Bifidobacterium genera[7]. While the adult microbiome is highly diverse, it also includes smaller populations of other bacterial groups, such as Proteobacteria, Verrucomicrobia, Actinobacteria, Cyanobacteria, and the genus Fusobacteria[8].

These observations underscore the microbiome's dynamic nature, which is continuously shaped by a combination of biological and environmental factors across the human lifespan. Understanding this developmental trajectory is crucial for advancing knowledge about the role of the microbiome in health and disease.

3. MECHANISMS LINKING GUT MICROBIOTA TO MENTAL HEALTH

3.1 GUT-BRAIN AXIS PATHWAYS

- Neural communication (vagus nerve and enteric nervous system)

The gut-brain axis embodies the dynamic and bidirectional communication between the central nervous system (CNS) and the enteric nervous system (ENS), mediated by intricate mechanisms and biochemical signals. Central to this system is the gut microbiota, which influences both gastrointestinal physiology and CNS function. Notably, while the brain is a pivotal component of this communication, the spinal cord also plays a crucial role, facilitating signal transmission between the nervous centers and the gut[9]. Although the full scope of mechanisms underlying gut-brain interactions remains to be elucidated, several key regulatory pathways have been identified. One prominent pathway involves the vagus nerve, the primary anatomical structure mediating communication within the gut-brain axis. Another critical pathway is the regulation of tryptophan metabolism, a precursor to serotonin, a neurotransmitter with a well-documented role in mood regulation and nervous system function[6]. Experimental studies have demonstrated that activation of the vagus nerve can produce significant anti-inflammatory effects. This activity helps protect against the development of leaky gut syndrome and reduces the risk of microbial sepsis.

The protective effect is mediated by the α7 subunit of the nicotinic acetylcholine receptor, highlighting specific molecular mechanisms underlying this response[6]. However, while the vagus nerve is essential, it is not the sole conduit for microbiota-brain interaction. Research has shown that vagotomy (surgical severance of the vagus nerve) does not significantly alter the effects of antimicrobial agents on brain function or behavior in experimental models. This finding indicates the presence of alternative, vagus-independent pathways that facilitate communication between the gut microbiota and the nervous system[6]. The gut-brain axis is, therefore, a highly complex and multifaceted system. Further research is needed to fully understand its physiological roles and to explore the therapeutic potential of modulating this axis for the treatment of both mental and somatic disorders.

- Endocrine pathways (hypothalamic-pituitary-adrenal axis)

The hypothalamic-pituitary-adrenal (HPA) axis is a critical component of the endocrine system, functioning through a negative feedback mechanism to maintain homeostasis. Its activation is essential for the body's adaptation to stressors and dynamic conditions. However, excessive or prolonged activation of the HPA axis has been implicated in various disorders, including endogenous depression. Notably, some theories suggest that psychotic depression represents a clinical manifestation of HPA axis dysregulation, underscoring the importance of investigating this system in the context of mental health disorders. A key factor stimulating the HPA axis is the presence of pro-inflammatory cytokines, whose elevated levels can result from gut dysbiosis—a disruption in the composition and function of the gut microbiota. Cytokines such as IL-1β, IL-6, and TNF-α trigger the hypothalamus to release corticotropin-releasing hormone (CRH), which in turn stimulates the pituitary gland to produce adrenocorticotropic hormone (ACTH). ACTH acts on the adrenal glands, leading to the secretion of cortisol, commonly known as the "stress hormone." Cortisol, through its negative feedback loop, helps regulate and limit excessive inflammatory responses. The recognition of these connections has sparked interest in the potential for modulating the HPA axis using probiotics, which may influence brain function and stress responses. For instance, a study investigating the effects of *Lactobacillus farciminis* on the neuroendocrine response to stress and plasma cytokine concentrations revealed promising results. Stress typically induces a rapid rise in plasma ACTH levels, noticeable within 15 minutes and persisting for up to 45 minutes. Surprisingly, stress did not significantly alter plasma levels of pro-inflammatory cytokines like IL-1β, IL-6, or TNF-α. However, treatment with *L. farciminis* effectively prevented the stress-induced increase in ACTH and corticosterone levels, indicating its potential role in modulating the HPA axis response to stress[10]. Notably, while *L. farciminis* suppressed the activity of the HPA axis, it did not affect the plasma cytokine profile, suggesting that its actions are specific to neuroendocrine regulation rather than broad immunomodulation. Beyond hormonal regulation, probiotics may exert neuroprotective effects, safeguarding against stress-induced synaptic damage. For example, a study conducted on rats demonstrated that just two weeks of probiotic treatment significantly reduced ACTH and corticosterone levels. These findings highlight the suppressive effect of probiotics on HPA axis activity and suggest their potential therapeutic application in managing chronic stress and depression[11]. This body of research emphasizes the promising role of probiotics as a novel approach to modulating the HPA axis, with implications for treating stress-related and depressive disorders. Further studies are necessary to clarify the mechanisms and optimize the clinical use of probiotics in this context.

- Immune-inflammatory pathways

The development of the intestinal microbiota begins during the perinatal period and, according to some research, may even start in utero. Environmental factors, including the mother's diet and microbiota, significantly influence the initial composition of the child's gut microbiota. Breastfeeding is particularly critical in this process, as it fosters the establishment of a beneficial microbiota. Human milk contains numerous components that support the growth of desirable microorganisms. Of special importance are human milk oligosaccharides (HMOs), which function as prebiotics by promoting the proliferation of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* spp. These bacteria optimize the composition of the infant's gut microbiome. In contrast, infants fed formula milk tend to have microbiota dominated by other bacteria, such as *Enterococcus*, *Bacteroides* spp., and *Clostridioides* spp[8]. Research has demonstrated a direct correlation between the concentration of secretory immunoglobulin A (IgA) in intestinal secretions and the abundance of bifidobacteria in the gut microbiota of infants. IgA plays a vital role in protecting mucosal surfaces from pathogenic organisms, with its levels being positively influenced by the presence of beneficial bacteria. Conversely, the concentration of the pro-inflammatory cytokine interleukin-6 (IL-6) in intestinal secretions has been observed to inversely correlate with the abundance of *Bacteroides fragilis*. Excessive inflammation in infancy, marked by elevated IL-6 levels, may increase the risk of gastroenteritis later in life[8]. Inflammation during infancy can compromise intestinal barrier integrity, leading to increased gut permeability. During inflammatory processes, mediators such as tumor necrosis factor-alpha (TNF-α) and monocyte chemoattractant protein (MCP) are released, which not only exacerbate gut permeability but also influence the permeability of the blood-brain barrier (BBB). This enhanced permeability facilitates the transfer of inflammatory signals and microbial metabolites into systemic circulation and the central nervous system, intensifying interactions within the gut-brain axis. Such disruptions may increase vulnerability to neuropsychiatric conditions like depression and anxiety disorders[3, 12]. Optimizing the composition of the gut microbiota from early life is crucial for promoting overall health. A balanced microbiota supports immune function, reduces inflammation, and strengthens the intestinal barrier. Moreover, a healthy microbiota may positively influence gut-brain axis mechanisms, potentially mitigating the risk of developing neuropsychiatric disorders later in life. Given the profound implications of gut microbiota on health, further research is essential to elucidate the mechanisms linking the microbiota and the nervous system. This understanding could pave the way for innovative therapeutic approaches. In particular, strategies to modulate the microbiota through dietary interventions, prebiotics, or probiotics hold promise as preventive and therapeutic tools for a variety of conditions.

3.2 MICROBIAL METABOLITES AND THEIR IMPACT ON THE CENTRAL NERVOUS SYSTEM

Bacteria inhabiting the human digestive tract play a key role in the production of numerous substances that affect the functioning of various organs throughout the body, including the central nervous system (CNS). This phenomenon is known as the gut-brain axis and is the subject of intensive research. In various health conditions, especially in the course of various pathologies, interactions between the gut microbiota and the brain may be intensified, disturbed

or modified. Although the mechanisms of the mutual interaction of this axis are still being thoroughly studied, some signaling pathways have already been well understood, especially in animal models. One of the better documented signaling pathways is the pathway associated with the mRNA of brain-derived neurotrophic factor (BDNF), which plays an important role in the dentate gyrus of the hippocampus. BDNF, which is one of the key neurotrophic factors, affects processes related to the perception of stress and connects endocrine, neural and immunological pathways in mammalian organisms. Its presence supports the development of neurons and synapses, which are key in the regulation of emotions, mood and cognitive processes, including memory and learning. In mice devoid of microorganisms, so-called germ-free mice, an increased stress response was observed, which was associated with a decrease in BDNF levels in the hippocampus. This phenomenon was reversed after recolonization of the mice's gut with strains of Bifidobacteria bacteria, suggesting that the gut microbiota has a direct impact on neurotrophic balance and the body's response to stress. Additionally, studies have shown that Bifidobacteria affect the expression of mRNA of GABA (gamma-aminobutyric acid) receptors, which may be crucial in regulating the stress response, and also change serum cortisol levels. Cortisol, a major stress response hormone, is closely linked to the functioning of the nervous system and its excessive production can lead to health disorders such as depression and anxiety. Interestingly, these changes did not occur when the mice underwent vagotomy, a procedure involving the severing of the vagus nerve[7]. This suggests that the parasympathetic nervous system (including the vagus nerve) plays an important role in transmitting signals from gut bacteria to the nervous system, which is crucial in regulating the stress response.

3.3 DYSBIOSIS AND ITS POTENTIAL ROLE IN PSYCHIATRIC CONDITIONS

Due to the enormous diversity of the intestinal microbiota, discussed in the introduction, defining the concepts of eubiosis and dysbiosis is a challenge. Dysbiosis is a disturbance in the composition or number of microorganisms inhabiting the gastrointestinal tract, which, through its numerous mechanisms of action on other organs, can lead to a wide range of symptoms. Although these symptoms are most often associated with the gastrointestinal tract, it is worth noting that dysbiosis can also have serious consequences for metabolic, autoimmune, and mental health, which is the main topic of this study. Of course, one cannot ignore typical intestinal symptoms, such as abdominal pain, diarrhea, flatulence, or constipation, which are

most common in cases of dysbiosis. Intestinal dysbiosis also results in increased permeability of the intestinal membrane, which leads to the so-called leaky gut syndrome[13]. In this condition, metabolites, bacterial molecules, and even bacteria themselves can pass in excess through the intestinal submucosa into the systemic circulation. This phenomenon has far-reaching health consequences, including contributing to the development of diseases such as IBD (inflammatory bowel disease), diabetes, asthma, as well as mental disorders, including depression, anxiety, and even autism[3]. It is also worth noting that bacteria are not the only microorganisms inhabiting our digestive tract that can affect the development of pathology in the case of dysbiosis. An example is Candida fungi, which in excess can limit the absorption of carbohydrates and minerals, and also lead to the overproduction of toxins. There are suggestions that imbalances in the intestinal microbiota, including an excess of Candida, may play a role in the pathogenesis of autism spectrum disorders[14]. Another condition of intestinal dysbiosis is SIBO (Small Intestinal Bacterial Overgrowth). In the case of this disorder, there is an abnormal colonization of the small intestine by bacteria, which can lead to disorders of tryptophan metabolism. Tryptophan is a precursor of serotonin, a neurotransmitter that is crucial for mental health. Reducing the availability of tryptophan in the body can exacerbate or even cause mental disorders, including depression and anxiety. Although there are many theories about the influence of SIBO on the development of mental problems, the full pathophysiology of this process has not yet been fully explained[15].

4. GUT MICROBIOTA AND DEPRESSION

4.1 MICROBIAL COMPOSITION IN INDIVIDUALS WITH DEPRESSION

Depression is a complex condition with a multifactorial background. Several key mechanisms can be distinguished in the pathogenesis of depression, including neuroplastic causes, organizational and structural changes, and neurochemical dysfunctions[12]. In recent years, more and more studies have indicated the role of gut microbiota disorders in the development of depression. It has been proven that the administration of bacterial endotoxins to healthy individuals who had no history of depressive disorders resulted in the release of inflammatory cytokines and the subsequent occurrence of classic depressive symptoms. These studies have shown a direct correlation between elevated levels of proinflammatory cytokines, such as IL-6 and TNF-α, and the occurrence of symptoms of depression and anxiety[16]. An interesting

result of this study is the fact that the administration of TNF-α alone to healthy patients did not cause depressive symptoms, which suggests that endotoxins, not TNF-α itself, were responsible for the occurrence of these symptoms. In the context of gut microbiota and depression, increasing evidence indicates that depression, at least in part, is inflammatory in nature. In particular, attention is paid to the chronic, low-grade inflammatory response, which may promote the development of depression. As part of this process, immune responses are activated, including cellular immunity and the activation of the compensatory anti-inflammatory reflex system (CIRS), which is characterized by abnormal, negative immunoregulatory processes. Therefore, all factors that promote chronic inflammation in the body may increase the risk of developing depressive disorders. One of the key elements of the pathogenesis of depression also turns out to be the body's immune response to LPS (lipopolysaccharide) derived from commensal Gram-negative bacteria. LPS is an endotoxin that is part of the outer cell membrane of Gram-negative bacteria. After entering the human body, LPS activates the immune system, leading to the release of proinflammatory cytokines, such as IL-1 or TNF-α. Studies have shown that people suffering from depressive disorders have higher concentrations of IgA and IgM antibodies directed against bacteria that are normal components of the human intestinal microflora, including *Hafnia alvei, Pseudomonas aeruginosa, Morganella morganii, Proteus mirabilis, Pseudomonas putida, Citrobacter koseri and Klebsiella pneumoniae [16]*.

4.2 EFFECTS OF PROBIOTICS AND PREBIOTICS ON DEPRESSIVE SYMPTOMS

Probiotics are live microorganisms, usually bacteria or yeasts, that are used as dietary supplements or components of other therapies, especially in the case of antibiotic treatment[10]. Their main purpose is to support the health of the intestinal microflora. Prebiotics, on the other hand, are specific substrates that are selectively used by microorganisms present in the host organisms, exerting a beneficial health effect. The most known and used prebiotics are fructooligosaccharides, such as inulin and oligofructose. In the context of mood disorders and depression, based on previous studies on the effect of intestinal microflora on mental health, the use of probiotics in the treatment of anxiety and depressive disorders is still in the phase of intensive research[10]. Considering depression as an inflammatory disease, it is worth noting that the documentation indicating the ability of probiotics to suppress inflammatory cytokines

[17]provides a solid argument for attempts to include them in the treatment of depression. Studies have shown that patients with chronic inflammation who took probiotics responded positively to them, which was manifested by a reduction in the production of TNF-α, one of the key pro-inflammatory cytokines[17]. Various studies on animal models have observed that the administration of the Bifidobacterium longum strain normalized anxiety-like behaviors, and chronic treatment with Lactobacillus rhamnosus led to a reduction in symptoms of anxiety and depression[10]. In turn, studies on humans also show promising results. In one of the experiments, after two months of administration of the Lactobacillus casei Shirota strain to patients suffering from chronic fatigue syndrome, a significant increase in the number of Lactobacillus and Bifidobacterium bacteria in the intestines was observed, as well as a significant decrease in anxiety symptoms compared to the control group. The use of probiotics also had a positive effect on improving brain activity. In addition, the use of L. helveticus R0052 and B. longum R0175 for just two weeks significantly alleviated symptoms of anxiety and depression in healthy volunteers, contributing to lower urinary cortisol (UFC) levels. In another study, after four weeks of consuming a fermented milk product with probiotics containing Bifidobacterium animalis subsp. lactis, Streptococcus thermophilus, Lactobacillus bulgaricus and Lactococcus lactis subsp. lactis, healthy women showed improved activity in brain areas responsible for processing emotions and sensations. These areas include the affective, visceral and somatosensory cortex. Although the mechanism of action of probiotics on mental health has not yet been fully elucidated, researchers postulate that probiotics may exert their therapeutic effects by influencing brain-derived neurotrophic factor (BDNF) and NMDA receptor 2a (NR2a) in the cerebral cortex and hippocampus[10]. Such interactions may support brain neuroplasticity, which is an important element in the treatment of mood disorders.

5. GUT MICROBIOTA AND ANXIETY DISORDERS

5.1 ANIMAL MODELS INVESTIGATING GUT MICROBIOTA AND ANXIETY

The relation between gut microbiota and mental health is a popular research topic. One of the most common disorders are anxiety disorders[18]. Brain development and brain health and its correlation with microbiota, known as the microbiota-gut-brain axis, has mostly been observed in animal models. Research is based on the observations made mostly with germ-free, antibiotic-treated, humanised and genetically modified mice[19]. Due to the complexity of the

axis, fewer clinical observations have been made in humans to compare the same relations recorded in rodents[20]. An animal study showed that the gut microbiome may influence anxiety-related behaviour in mice[21], which leads to another study, that remarked a significantly lower levels of *Firmicutes* in mice presenting higher anxiety[22]. Animal models still provide crucial theories that are yet to be confirmed in clinical studies.

5.2 CLINICAL STUDIES ON GUT MICROBIOTA IN ANXIETY PATIENTS

As mentioned above, there's still little clinical research, yet the available data is promising. For example, a study of 190 Spanish anxiety patients showed that anxiety individuals had lowered Simpson's Diversity Index (a measure of species abundance) in the gut microbiome[23]. Another study that observed change in microbial richness and diversity in general anxiety disorder patients, also observed reduced levels of *Firmicutes* and bacteria producing SCFAs, *Fusobacteria* and *Bacteroidetes* in particular[24]. In patients with social exclusion, being one of anxiety disorder manifestations, an increase of the abundance of *Prevotella* was observed, whereas the abundance of *Faecelibacterium* spp. and *Firmicutes/Bacteroidetes* ratio was significantly decreased[25]. A study of 68 students with anxiety showed that the alteration of gut microbiota, after supplementation of *Lactobacillus plantarum* (JYLP-326), could help alleviate the symptoms of anxiety and depression. The supplementation helped restore dysbiosis which was the result of chronic stress and anxiety[26].

5.3 CHALLENGES IN TRANSLATING FINDINGS TO CLINICAL PRACTICE

Difficulties in comparing animal and clinical studies are commonly known to researchers. The complexity of the microbiota-gut-brain axis makes it especially challenging to find significant correlation between the gut microbiome and, not only anxiety, but the majority of mental health problems. The findings in animal models are promising, yet we still have a lot to dive into to be able to understand the axis well and use the knowledge in clinical practice. However, the more research on microbiota diversity changes emerges, the more individuals meet the including criteria for future studies.

6. MICROBIOTA TRANSFER THERAPY (MTT)

6.1 DEFINITION AND PROCESS OF MICROBIOTA TRANSFER THERAPY

The procedure involves transferring healthy bacteria (microbiota) from the feces of a thoroughly screened donor into the recipient's colon. This is typically performed via colonoscopy but can also be carried out using upper endoscopy. Due to the absence of universally standardized laboratory protocols, sample size guidelines vary widely, ranging from 30 to 100 grams (1.1 to 3.5 ounces) of fecal material for effective treatment. To preserve bacterial viability, fresh stool is utilized, with preparation occurring within 6–8 hours of collection. Preparation methods differ between facilities; some use a mortar and pestle, while others prefer a blender. The resulting mixture is filtered and stored in a container for administration. To ensure safety, all handling and administration are conducted in a clinical environment. Once suspended, the transplant material may be delivered via nasogastric or nasoduodenal tubes, a colonoscope, or as a retention enema[27].

FMT is considered a safe and well-tolerated therapeutic strategy. In a 2023 study assessing patients' perceptions of the procedure, no significant adverse events were reported between the placebo and control groups. Following treatment, 80% of patients indicated they would consent to the procedure again if necessary[28].

6.2 EVIDENCE FOR MTT IN MENTAL HEALTH DISORDERS

Research has demonstrated a bidirectional relationship between gut microbiota and depression in rodent models. Alterations in microbial composition, particularly the depletion of *Lactobacillus* and an increase in *Akkermansia*, were linked to neuroinflammatory activity and played a significant role in the onset of depression. Considering the limitations of current pharmacological interventions, scientists have explored the effects of microbiota transfer on gut microbiota, behavior, and brain function. These findings provide scientific backing for employing this approach in treating major depressive disorder[29].

Jiang et al. conducted a study evaluating patients with COVID-19 and found that FMT significantly reduced depressive symptoms in the control group. Additionally, it alleviated gastrointestinal symptoms associated with COVID-19[30]. In patients with irritable bowel syndrome (IBS), FMT led to reductions in depression and anxiety symptoms, as assessed using the Hamilton Anxiety and Depression Scales (HAM-A and HAM-D)[31]. Case studies have

also reported using FMT as an adjunctive therapy for severe depression. After four weeks, patients showed significant improvement, which persisted for up to eight weeks, alongside a reduction in constipation frequency[32].

7. FACTORS INFLUENCING GUT MICROBIOTA AND MENTAL HEALTH

7.1 STRESS AND LIFESTYLE FACTORS

It is commonly known that stress and lifestyle-related factors have great impact on our well-being. There is research that shows these factors also impact the gut microbiota, which, as already determined, secondarily affects mental health. Even though stress directly intereferes gut microbiota, the other way around, dysbiosis itself can be a factor leading to chronic stress symptoms and further cascade of decreased microbiota diversity[33]. A study in rodents shows that oral supplementation of *Lactobacillus* modulates their stress and cognition behaviour[34]. Physical exercise, as a form of lifestyle-related factor, according to a systematic review, positively affects the microbiota in humans, increasing butyrate-producting bacteria, particularly *Roseburia hominis*, *Faecalibacterium pausnitzii* and *Ruminococcaceae[35]*.

7.2 ANTIBIOTICS

Administration of antibiotics heavily affects the microbiome of a human intenstinal tract, often leading to transient or permanent dysbiosis requiring probiotic intake or even faecal transfers. Clinical trials show that exposure to antibiotic, especially penicillin and quinolones, may lead to increased risk of anxiety which is associated with microbiota diversity changes[36]. Another study regarding quinolones reports psychiatric events, such as anxiety and depression disorder, in 62%-72% patients who took fluoroquinolones. Such observations were also made in mice and in both cases the main speculation of the cause would be impairment of gut microbiota as a result of antibiotic intake[37, 38]. This correlation between antibiotic use and dysbiosis comes as no surprise, knowing the mechanism of the medications and the existence of microbiota-gut–brain axis.

8. THERAPEUTIC POTENTIAL OF MODULATING GUT MICROBIOTA

8.1 PROBIOTICS, PREBIOTICS, AND SYNBIOTICS

Emphasizing the critical role of the gut-brain axis in mental health, growing research indicates that probiotics, especially those from the *Lactobacillus* genus, may help prevent and manage these conditions by influencing gut microbiota. For example, animal model studies have found that *Lactobacillus murine* (L. murine) and *Lactobacillus reuteri* (L. reuteri) increase gamma-aminobutyric acid (GABA) levels in the hippocampus, alleviating depression-like symptoms in Dcf1 knockout mice[39]. Similarly, the probiotic *Pediococcus acidilactici* CCFM6432 has been shown to reduce stress-induced anxiety-like behaviors by suppressing the overgrowth of *Escherichia shigella* and supporting *Bifidobacterium* growth in C57BL/6 mice[40]. Human studies also support these findings, with one involving 423 women in New Zealand showing that *Lactobacillus rhamnosus* HN001 significantly lowered postpartum depression and anxiety scores[41]. Additionally, synbiotics, which combine probiotics and prebiotics, have demonstrated potential in reducing the side effects of antipsychotic drugs, such as olanzapine-related weight gain and insulin resistance in psychiatric patients. This expanding body of evidence highlights the potential of probiotics and synbiotics as innovative approaches to mental health treatment[42].

8.2 DIET-BASED INTERVENTIONS

Research has demonstrated that early-life diets enriched with bioactive milk fractions and prebiotics can reduce anxiety-related behaviors in juvenile rats. These diets were also found to increase *Lactobacillus* spp., a change positively associated with altered expression of serotonin (5-HT)1A and 5-HT2C mRNA, highlighting a potential link between gut microbiota and brain chemistry[43]. Similarly, a combination of almond baru (*Dipteryx alata Vog.*) and goat whey was shown to modulate gut microbiota by reducing harmful bacteria like *Clostridia_UCG-014*, which contributed to improved memory and reduced anxiety in rodents[44]. Another study on mice revealed that Chaihu-Shugan-San, a traditional herbal mixture, alleviated anxiety and depression caused by restraint stress. This effect was achieved by reversing stress-induced gut microbiota imbalances and promoting BDNF expression through an NF-κB-dependent mechanism[45]. Additionally, the Mediterranean diet has been found to support gut health by reducing inflammatory and pathogenic bacteria like *Escherichia coli* while increasing beneficial commensal bacteria, such as *Bifidobacteria[46]*. These findings underscore the possible influence of diet and natural interventions on mental health through the gut-brain axis.

8.3 FUTURE PERSPECTIVES ON GUT-BRAIN THERAPIES

Recent studies suggest that the gut microbiota plays a significant role in the gut-brain axis. Emerging evidence indicates that the microbiota can influence brain function and mental health through mechanisms such as immune modulation, production of neurotransmitters, and the regulation of stress responses. While promising, much of this research is still in its early stages, with many findings derived from animal studies. Human trials are increasingly being conducted to evaluate the potential therapeutic benefits of modulating the gut microbiota in psychiatric conditions such as depression and anxiety. If these trials yield positive results, supplementation with probiotics or other microbiota-targeted interventions, like elimination of certain bacteria with antibiotics, could become a novel approach in psychiatric treatment. However, further evaluation is needed to establish efficacy, safety, and the precise mechanisms involved.

9. LIMITATIONS AND GAPS IN CURRENT KNOWLEDGE

Despite significant advances in understanding the microbiome and its impact on mental health, further research is essential to thoroughly investigate this relationship and evaluate its therapeutic potential. One of the main challenges lies in the vast diversity of organisms comprising the gut microbiota, many of which remain insufficiently studied, making it difficult to fully assess their effects on human functioning. Another complicating factor is the high variability of gut microbiota composition, which differs not only between individuals but also across various disease states, dietary changes, and stages of life.

Financial constraints also pose a limitation, as analyzing the gut microbiome and evaluating individual organisms in terms of quantity, species, strain, or number is an expensive endeavor. While there is an abundance of fundamental research assessing the influence of gut microbiota on specific molecules and metabolic processes, a deeper understanding of these correlations could, in the future, facilitate the development of more robust and better-designed studies. Such studies would directly evaluate the microbiome’s impact on anxiety and depression.

Unfortunately, current research often involves small clinical cohorts, which makes it challenging to draw comparisons between studies and generalize findings.

10. CONCLUSIONS

The gut microbiota plays a crucial role in the functioning of the gut-brain axis, with its impact on mental health increasingly well understood. Scientific evidence suggests that the gut microbiota influences brain function and mental health through mechanisms such as immune modulation, neurotransmitter production, and stress response regulation. Disruptions in the microbiota composition, such as dysbiosis, can contribute to inflammation, increased intestinal permeability, and changes in brain neuroplasticity, potentially increasing the risk of depression and anxiety disorders. Clinical studies and animal experiments provide evidence that interventions like the use of probiotics, synbiotics, or dietary changes can alleviate symptoms of mental disorders, reduce cortisol levels, and enhance brain activity in regions responsible for emotions and perception. Moreover, research on specific bacterial strains, such as *Lactobacillus* and *Bifidobacterium*, demonstrates their therapeutic potential in reducing anxiety and depression. However, much of this evidence originates from animal studies, emphasizing the need for further research in humans. Technological advancements have deepened our understanding of the microbiota, but its immense diversity, high interindividual variability, and the financial constraints of biological analyses present significant challenges. Factors such as lifestyle, diet, and changes in the microbiota at different life stages must also be considered when interpreting research findings.

In conclusion, the gut microbiota may play a significant role in modern therapeutic approaches for treating depression and anxiety disorders. While the initial findings are promising, further well-designed studies involving larger clinical cohorts are essential to confirm the efficacy, safety, and mechanisms of such interventions.

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