

Relationship Between Microbiota and Mental Health: A Holistic View

Mikrobiyota ve Ruh Sağlığı İlişkisi: Bütüncül Bir Bakış

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ABSTRACT

The microorganisms in the human intestine regulate brain function and mental health through the microbiota-gut-brain axis. This bidirectional communication network encompasses neural (e.g., vagus nerve), endocrine (e.g., cortisol, serotonin), immune (e.g., cytokines), and microbial metabolite (e.g., short-chain fatty acids) pathways. Recent studies highlight the role of gut dysbiosis in the pathogenesis of psychiatric disorders such as depression, anxiety, autism spectrum disorders, schizophrenia, bipolar disorder, and post-traumatic stress disorder. Altered microbial profiles—marked by reduced microbial diversity, depletion of beneficial short-chain fatty acids-producing bacteria, and increased pro-inflammatory taxa—have been consistently associated with neuropsychiatric symptomatology. Studies have shown that microbiota interventions such as probiotics, prebiotics and dietary changes can affect mental health, giving rise to the concept of 'psychobiotics'. This narrative review presents a comprehensive synthesis of the mechanistic underpinnings linking gut microbiota to psychiatric disorders and evaluates the therapeutic potential of microbiota-based strategies. It also explores new developments such as tailored psychobiotic treatments, biomarkers derived from the gut microbiota, and their practical applications in psychiatric care. By adopting an integrative perspective, this review aims to bridge disciplines and foster the development of holistic mental health care approaches grounded in the dynamic interplay between the gut and the brain.

Keywords: Microbiota-gut-brain axis, psychobiotics, psychiatric disorders, mental health

Öz

İnsan bağırsağındaki mikroorganizmalar, mikrobiyota-bağırsak-beyin eksenini aracılığıyla beyin işlevlerini ve ruh sağlığını düzenlemektedir. Bu çift yönlü iletişim ağı; sinirsel (örn. vagus siniri), endokrin (örn. kortizol, serotonin), immün (örn. sitokinler) ve mikrobiyal metabolit (örn. kısa zincirli yağ asitleri) yollarını kapsamaktadır. Son dönem çalışmalar, bağırsak mikrobiyotasındaki dengesizliğin depresyon, anksiyete, otizm spektrum bozuklukları, şizofreni, bipolar bozukluk ve travma sonrası stres bozukluğu gibi psikiyatrik bozuklukların patogeneğinde rol oynadığını ortaya koymaktadır. Azalmış mikrobiyal çeşitlilik, yararlı kısa zincirli yağ asidi üreten bakterilerin tükenmesi ve proinflatuvar taksonların artışı ile karakterize olan değişmiş mikrobiyal profillerin, nöropsikiyatrik semptomatoloji ile tutarlı biçimde ilişkili olduğu saptanmıştır. Çalışmalar, probiyotikler, prebiyotikler ve diyet değişiklikleri gibi mikrobiyota temelli müdahalelerin ruh sağlığı üzerinde etkili olabileceğini göstermekte; bu da "psikobiyotikler" kavramının ortaya çıkmasına yol açmaktadır. Bu derleme, bağırsak mikrobiyotası ile psikiyatrik bozukluklar arasındaki ilişkiyi açıklayan mekanistik temellere dair kapsamlı bir sentez sunmakta ve mikrobiyota temelli stratejilerin terapötik potansiyelini değerlendirmektedir. Ayrıca, kişiye özel psikobiyotik tedaviler, bağırsak mikrobiyotasından türetilmiş biyobelirteçler ve bunların psikiyatrik bakımda pratik uygulamaları gibi yeni gelişmeleri de incelemektedir. Bütüncül bir bakış açısını benimseyen bu çalışma, disiplinler arası etkileşimi güçlendirmeyi ve bağırsak ile beyin arasındaki dinamik ilişkinin temellerine dayalı bütüncül ruh sağlığı yaklaşımlarının gelişimine katkı sağlamayı amaçlamaktadır.

Anahtar sözcükler: Mikrobiyota-bağırsak-beyin eksenini, psikobiyotikler, psikiyatrik bozukluklar, ruh sağlığı

Introduction

Microbiota is the name given to all microorganisms (bacteria, viruses, fungi, and archaea) living in a specific environment. The microbiota, which is especially concentrated in the intestines in the human body, functions like an additional organ with approximately trillions of microorganisms and affects the physiology of the body in various ways like a metabolic machine (Khan et al. 2025). The concept of the gut-brain axis refers to the bidirectional communication between the gut microbiota and the central nervous system. In this axis, a continuous exchange of information occurs via neural (e.g., via the vagus nerve), hormonal, and immune pathways (Kodidala et al. 2024). In these ways, microbiota can modulate brain functions by affecting neurotransmitter production, hormonal balances, and immune responses.

Recent studies have shown that imbalances in the gut microbiota may be associated with various neuropsychiatric disorders such as depression, anxiety, autism, and schizophrenia (Delanote et al. 2024). Although mental health disorders have traditionally been viewed as diseases originating solely from the central nervous system, current findings reveal a strong connection between psychiatric conditions and the gastrointestinal system. For example, gastrointestinal symptoms are among the most common physical complaints in individuals with depression; similarly, anxiety disorders frequently accompany intestinal disorders such as irritable bowel syndrome. In addition, antidepressant medications and psychotherapy can alleviate not only mental symptoms but also intestinal-related problems (McGuinness et al. 2022). All these findings show that the relationships between mental health and gut microbiota are clinically important. Scientific interest in the link between microbiota and mental health began in the early 2000s and initially attracted attention with findings obtained in animal models. Especially since the early 2010s, hypotheses suggesting a link between the microbiota and brain development, behavior, and psychiatric disorders have gained traction, and this field has rapidly developed around the concept of the "microbiota-brain axis". Initially considered speculative, this relationship has gained scientific basis with the increasing number of human-based studies and systematic reviews since 2015. Today, it is positioned as a multidisciplinary research area at the intersection of psychiatry, neuroscience, microbiology, and nutritional sciences.

This review aims to examine the interaction between the microbiota and mental health from a holistic perspective. First, the communication pathways between the gut and brain (via neural, endocrine, immune, and microbial metabolites) will be detailed. Then, the relationships between changes in the gut microbiota and psychiatric conditions such as depression, anxiety, autism spectrum disorders, schizophrenia, bipolar disorder, and post-traumatic stress disorder (PTSD) will be examined in light of current literature. Studies examining the effects of microbiota interventions (probiotics, prebiotics, diet, etc.) on mental health will be evaluated, as will the concept of psychobiotics. Finally, critical debates, limitations, future research directions, and their implications for clinical practice will be discussed, providing a comprehensive overview of the microbiota-mental health axis.

As part of this literature review, English and Turkish articles published between 2010 and 2025 were examined. Studies were searched through PubMed, Scopus, Web of Science, and Google Scholar databases. Keywords such as "gut microbiota," "psychobiotics," "psychiatric disorders," "microbiota-gut-brain axis," "mental health," "depression," "anxiety," "autism," "schizophrenia," "bipolar disorder," and "PTSD" were used. Priority was given to systematic reviews, meta-analyses, and original studies with high impact factors in the evaluation; findings were synthesized qualitatively and structured with an interdisciplinary approach.

Communication between Gut Microbiota and Brain

Communication between gut microbiota and brain occurs bidirectionally via multiple biological pathways. This section examines the main communication mechanisms.

Neural Pathways (Vagus Nerve and Enteric Nervous System)

One of the fastest and most direct communication pathways between the gut and the brain is neural

transmission. The vagus nerve, in particular, plays a critical role in this axis. The vagus nerve is like a “signal highway” that carries most of the information circulating in the body from the gut to the brain; approximately 80% of its sensory fibers are afferent (i.e., carry information from the gut to the brain). Gut microbiota can stimulate the vagus nerve through some molecules it produces and the intestinal nerve cells it interacts with (Mendez-Hernandez et al. 2025). For example, in a classic experiment conducted on mice, it was shown that the probiotic *Lactobacillus rhamnosus* reduced anxiety-like behaviors, but this effect was eliminated when the vagus nerve was cut (Bravo et al. 2011). This finding emphasizes the importance of the vagus nerve in transmitting microbiota-derived signals to the brain. In addition, the enteric nervous system, also known as the “second brain” located in the intestine, directly interacts with the central nervous system with hundreds of millions of nerve cells (McGuinness et al. 2022). Signals originating from the enteric nervous system are transmitted to the brain via the vagus nerve and spinal nerves, and can affect mood, stress response, and behavior.

Endocrine Pathways (Hormones: Cortisol, Serotonin, etc.)

The endocrine system, or hormonal communication, also has an important place in the microbiota-brain axis. The stress hormone cortisol is secreted via the hypothalamic-pituitary-adrenal (HPA) axis and affects both brain and gut functions. The microbiota has been shown to play a role in regulating the HPA axis: Germ-free animals raised in sterile conditions show an excessive cortisol response to stress compared to normal animals; however, this abnormal stress response is corrected when colonized with beneficial bacteria early on (Sudo et al. 2004). This suggests that a healthy microbiota is critical for balancing stress hormones. The microbiota also affects the body’s production of serotonin. Approximately 90% of body serotonin is secreted by enteroendocrine cells in the gut, and the microbiota acts as an important stimulator in this process (Yano et al. 2015). Some intestinal bacteria affect the serotonergic system by altering the metabolism of the amino acid tryptophan. For example, a group of spore-forming bacteria abundant in the gut can increase the release of serotonin from enteroendocrine cells. Although serotonin cannot directly cross the blood-brain barrier, it can be converted into nerve signals via receptors at the vagus nerve endings or can indirectly affect brain function by regulating intestinal movements and inflammation. Microbiota can also produce neuroactive substances such as dopamine, GABA (gamma-aminobutyric acid), and acetylcholine or modulate their levels (Delanote et al. 2024). For example, some *Lactobacillus* species produce GABA, while *Escherichia* species can synthesize norepinephrine; these molecules can communicate with the brain via the intestinal nervous system (Huang et al. 2022). In this way, microbiota exerts its effect on mood, anxiety, and cognitive functions through endocrine and neurochemical pathways (Delanote et al. 2024).

Interaction through the Immune System

The immune system is another critical communication pathway of the gut-brain axis. The gut is one of the largest immune organs in the body, and the immune cells there are in constant interaction with the microbiota. A healthy microbiota maintains immune homeostasis in the intestinal mucosa and prevents excessive inflammatory responses. In the case of dysbiosis, the integrity of the intestinal barrier can be disrupted and a “leaky gut” can occur; in this case, toxic molecules in the gut (e.g. bacterial lipopolysaccharide, LPS) enter the circulation, causing chronic low-level inflammation in the body (Delanote et al. 2024). Many markers of inflammation are known to be elevated in disorders such as depression and schizophrenia. Indeed, one of the most consistent findings of dysbiosis seen in depression is the decrease in anti-inflammatory beneficial bacteria and the increase in pro-inflammatory bacteria (Liu et al. 2023). Chronic inflammation caused by microbiota can affect the brain through messenger molecules called cytokines; for example, elevation of cytokines such as IL-6 and TNF-alpha can lead to neuroinflammation in the brain, contributing to depressive and anxiety-like behavioral changes (Ting et al. 2020, Zhu et al. 2020). In addition, peripheral inflammation can disrupt the functioning of stress hormone receptors in the brain, alter neurotransmitter balance, and activate brain immune cells called microglia, affecting nerve cell functions (Sălcudean et al. 2025). As a result, an unhealthy microbiota profile can transmit negative signals to the brain via the immune system, putting mental health at risk; conversely,

psychological stress and mental disorders can also alter the microbiota through immune responses (bidirectional effect).

Microbial Metabolites (Short-Chain Fatty Acids and Others)

The gut microbiota produces a variety of metabolites as they break down nutrients, some of which can affect brain function. One of the best-studied examples is molecules such as acetate, propionate, and butyrate, called short-chain fatty acids (SCFAs). These fatty acids are formed when the microbiota ferments dietary fibers and, in addition to being the primary energy source for intestinal cells, they also enter the bloodstream and exert widespread effects throughout the body (Dalile et al. 2019). Butyrate is particularly known for its anti-inflammatory effects and intestinal barrier integrity-enhancing properties; it also has neuroactive effects on the brain. Butyrate has been shown to alter gene expression by inhibiting the histone deacetylase enzyme in brain cells, thereby producing antidepressant-like effects (Sun et al. 2018). SCFAs can also reach brain regions directly by stimulating vagal nerve receptors or partially crossing the blood-brain barrier. For example, it has been suggested that high levels of propionate may cause autism-like neurological effects in some individuals (Hsiao et al. 2013).

Another important group of metabolites produced by the microbiota are secondary bile acids; these are formed by the modification of liver-derived bile acids by bacteria and can affect neurological functions through receptors such as TGR5 and FXR in the brain. Tryptophan metabolites are also a critical intermediary (Cryan et al. 2019). The microbiota indirectly shapes the neurotransmitter balance by influencing whether the amino acid tryptophan is directed to serotonin or the kynurenine pathway in the body. For example, in the case of intestinal dysbiosis, the breakdown of tryptophan into neurotoxic kynurenines instead of serotonin may increase, which is thought to be a factor that increases the risk of depression. As a result, metabolites produced by the microbiota act as chemical messengers for both peripheral organs and the central nervous system. In fact, it has been reported in animal experiments that microbial metabolites (e.g. butyrate supplementation) taken from a healthy donor can alleviate depression and anxiety-like behaviors (Agus et al. 2018). In summary, neural connections such as the vagus nerve, hormonal signals such as cortisol and serotonin, immune factors such as cytokines, and microbial metabolites such as SCFAs form a multilayered communication network between the gut microbiota and the brain (Delanote et al. 2024). Thanks to this network, a change in the gut can affect brain function and therefore mood and behavior. Similarly, a change in the central nervous system (e.g. chronic stress) can also change the composition and activities of the gut microbiota through feedback. This complex network of interactions reveals the critical role of the gut-brain axis in mental health.

Microbiota and Psychiatric Disorders

Evidence is rapidly accumulating on the relationship between gut microbiota and various psychiatric disorders. This section will discuss microbiota changes and possible mechanisms detected in different clinical conditions, from depression and anxiety disorders to autism spectrum disorder, schizophrenia to bipolar disorder and PTSD. Findings on the relevant disorder are summarized under each subheading; at the end of the section, levels of evidence are comparatively evaluated.

Depression

Microbial Changes

Depressive disorders are a subject of intense interest in microbiota research. Significant differences have been identified in the gut microbiota of individuals diagnosed with major depression compared to healthy individuals (Liu et al. 2023). While many studies have reported decreased alpha diversity (the microbial richness and balance within an individual), a systematic review of 44 studies conducted by McGuinness et al. (2022) found no consistent difference in this regard. However, significant differences in beta diversity (the difference in microbial composition between groups) have been consistently reported between groups. The microbial profile associated with depression has been found to include decreases in beneficial

bacteria, particularly butyrate-producing *Faecalibacterium* and *Coprococcus*, and increases in inflammatory species, such as *Bacteroides* (Valles et al. 2019, Cheung et al. 2019). Furthermore, an increase in the *Eggerthellae* genus has also been associated with depression (Liu et al. 2023).

Mechanisms

A decrease in bacteria that produce short-chain fatty acids (SCFAs) such as butyrate can lead to a weakened intestinal barrier and increased inflammation. This process can trigger depressive symptoms by affecting the central nervous system via the gut-brain axis. Increases in pro-inflammatory bacteria and decreases in anti-inflammatory species are associated with cytokine imbalance and neuroinflammation (Liu et al. 2023).

Preclinical Evidence

Animal studies suggest that disruptions in the microbiota can cause depressive behaviors. Zheng et al. (2016) reported that transplanting microbiota from individuals diagnosed with depression into germ-free rats resulted in anhedonia and depression-like behaviors. Similarly, Kelly et al. (2016) observed increased anxiety and depressive symptoms in mice. These findings suggest that microbiota changes may play a causal role.

Clinical Evidence

Similar patterns have been identified in the microbiota in human studies. McGuinness et al. (2022) reported significant differences in beta diversity, while Cheung et al. (2019) highlighted an increase in inflammatory bacteria and a decrease in anti-inflammatory species. These findings support the relationship between depression and the microbiota at the clinical level.

Bidirectional Effects

Depression is a condition that not only affects the microbiota but is also affected by it. Depression-related factors such as loss of appetite, irregular eating habits, gastrointestinal disorders, and antidepressant use can disrupt microbial balance (Kelly et al. 2016, Zheng et al. 2016, Liu et al. 2023). Thus, a cyclical interaction may emerge in which depression increases dysbiosis, which in turn exacerbates depressive symptoms.

Anxiety Disorders

Microbial Alterations

Anxiety disorders are another psychiatric disorder thought to be strongly associated with the gut microbiota. Studies in individuals with this disorder have begun to identify a dysbiotic microbiota profile similar to depression. A decrease in microbial diversity and a decrease in the number of beneficial butyrate-producing bacteria are particularly striking (Simpson et al. 2021). It has been shown that in individuals with generalized anxiety disorder, butyrate-producing bacteria such as *Faecalibacterium* are reduced, while some lactic acid-producing bacteria such as *Lactobacillus* are increased (Jiang et al. 2018). These changes reveal a structural imbalance in the microbiota and its potential functional implications.

Mechanisms

Microbial alterations observed in anxiety disorders have been linked to mechanisms such as increased inflammation and changes in neurotransmitter production. A decrease in butyrate-producing bacteria may lead to a weakening of the intestinal barrier and the triggering of systemic and central inflammation. At the same time, the gut microbiota can alter central nervous system functions by affecting the production of neurotransmitters such as serotonin, GABA, and dopamine. These biological processes may contribute to the emergence of anxiety symptoms.

Preclinical Evidence

Animal models provide important preliminary data supporting the relationship between microbiota and anxiety. In particular, transplanting microbiota from individuals diagnosed with social anxiety into mice led

to increased social anxiety-like behaviors in these mice (Ritz et al. 2024). Such transplantation experiments suggest that the gut microbiota is not only correlated with anxiety but can also potentially trigger behavioral changes.

Clinical Evidence

Increasing numbers of human studies demonstrate altered microbiota profiles in anxiety disorders. Some studies examining depression and anxiety together report similar dysbiotic patterns in the two disorders, but also observe specific bacterial differences (Cheung et al. 2019). While a deficiency of beneficial SCFA-producing bacteria is prominent in both cases, the specific bacteria affected may vary across studies. Furthermore, according to a meta-analysis conducted by Musazadeh et al. (2023), probiotic supplements were found to be effective in reducing symptoms of depression, especially when administered for more than 8 weeks and at adequate doses. These findings support microbial interventions with potential therapeutic benefits for anxiety.

Bidirectional Effects

The relationship between microbiota and anxiety is bidirectional. Anxiety disorders can negatively impact microbial composition through changes in diet, impaired intestinal motility, and stress hormones. At the same time, dysbiosis in the microbiota can exacerbate anxiety symptoms through neuroinflammation and metabolic signaling. This interplay suggests a complex and cyclical relationship between anxiety and the microbiota.

Autism Spectrum Disorders

Microbial Alterations

Autism spectrum disorders (ASD) are another neurodevelopmental condition in which a strong link with the gut microbiota has been suggested. Interest in this area was initially driven by the high prevalence of gastrointestinal (GI) problems such as chronic constipation, diarrhea, bloating, and reflux in children with ASD (Młynarska et al. 2025). GI complaints are reported to be several times more common than in neurotypical peers, and the severity of GI symptoms often parallels the severity of autistic features (Karagözlü et al. 2022, Gan et al. 2023). Studies examining fecal microbiota profiles consistently report a dysbiotic composition in ASD compared with neurotypical controls, even though the exact bacterial taxa that differ vary across studies due to methodological and population differences (Korteniemi et al. 2023). Some recurring patterns include a reduced Bacteroidetes/Firmicutes ratio—i.e. relatively lower Bacteroidetes and higher Firmicutes—as well as increased abundance of Lactobacillus species and a slight rise in sulfate-reducing bacteria such as Desulfovibrio (Strati et al. 2017, Młynarska et al. 2025).

Mechanisms

The microbial changes observed in ASD may influence both gut physiology and brain development. An imbalance in Firmicutes and Bacteroidetes and an overrepresentation of bacteria such as Desulfovibrio can contribute to altered fermentation patterns, increased hydrogen sulfide production, and mucosal inflammation, which may underlie the frequent GI symptoms in ASD (Strati et al. 2017, Młynarska et al. 2025). Disruption of the intestinal barrier and low-grade inflammation may, in turn, affect the developing brain through immune, metabolic, and neural pathways along the gut-brain axis. These processes provide a plausible biological link between intestinal dysbiosis, GI complaints, and neurodevelopmental and behavioral features in ASD.

Preclinical Evidence

Animal models provide important mechanistic support for a causal contribution of the microbiota to ASD-like behaviors. In seminal experiments, colonization of germ-free mice with microbiota derived from individuals with ASD or with ASD-mimicking microbial/metabolite profiles has been shown to induce social deficits, repetitive behaviors, and altered communication, together with changes in brain signaling

pathways (Hsiao et al. 2013). Such transplantation and metabolite-focused studies indicate that specific microbial configurations can drive ASD-relevant phenotypes rather than merely co-occurring with them.

Clinical Evidence

Clinical studies reinforce the association between ASD and altered gut microbiota. Questionnaire-based and clinical assessments show that children and adolescents with ASD experience significantly higher rates of constipation, diarrhea, and other GI symptoms compared with neurotypical controls, and that GI symptom burden often correlates with ASD symptom severity (Karagözlü et al. 2022, Gan et al. 2023). Multiple fecal microbiome studies report consistent dysbiotic signatures, such as reduced Bacteroidetes/Firmicutes ratios, increased Lactobacillus, and elevated Desulfovibrio in ASD cohorts (Strati et al. 2017, Kortenien et al. 2023, Młynarska et al. 2025). Although not all findings fully overlap, the overall body of evidence supports the presence of ASD-specific microbial patterns.

Schizophrenia

Microbial Changes

Schizophrenia is a serious psychiatric disorder in which genetic and environmental factors play a role in its etiology. Recent research has shown significant differences in the gut microbiota of individuals diagnosed with schizophrenia compared to healthy individuals (Severance et al. 2016). Some studies have found a decrease in microbial diversity, particularly in beneficial bacteria such as Faecalibacterium. However, increased levels of certain genera such as Lactobacillus and Prevotella have been reported (Zhu et al. 2020). These changes suggest the existence of a unique dysbiotic profile associated with schizophrenia.

Mechanisms

It is thought that the microbial changes observed in schizophrenia may have effects not only at the intestinal level but also at the neurochemical and behavioral levels. Disturbances related to neurotransmitter systems such as glutamate and GABA are particularly noteworthy. In mouse models, brains colonized with microbiota transplanted from schizophrenia patients exhibited decreased glutamatergic activity and increased GABA levels (Zheng et al. 2016). These changes suggest potential mechanisms mediated by the microbiota in brain function and gene expression (Wei et al. 2024).

Preclinical Evidence

Strong data on the relationship between schizophrenia and microbiota have been obtained from preclinical animal studies. In a 2024 study, gut microbiota from schizophrenia patients was transplanted into sterile mice, resulting in behavioral abnormalities similar to schizophrenia (Wei et al. 2024). These behaviors included decreased social interaction and hyperactivity. Changes in the expression of genes associated with schizophrenia and neurotransmitter imbalances were also detected in the same mice.

Clinical Evidence

Similar findings have been observed in human studies. In a small-scale study, probiotic supplements containing Lactobacillus and Bifidobacterium given to patients with schizophrenia improved gastrointestinal symptoms and slightly reduced negative symptoms of the disease (Dickerson et al. 2014). Such findings highlight the potential benefits of microbiota-targeted interventions in schizophrenia. However, limitations such as sample size and study duration limit the generalizability of these findings.

Bidirectional Effects

The relationship between schizophrenia and the microbiota is not unidirectional. Unbalanced eating habits, metabolic syndrome, and antipsychotic medication use, which are common in patients with schizophrenia, can alter the microbiota. Olanzapine, a second-generation antipsychotic, in particular, causes changes in the gut microbiota that can trigger weight gain and insulin resistance (Qian et al. 2023). This complicates interpretations of whether microbiota changes in schizophrenia are a cause or a

consequence. Nevertheless, the complex and cyclical relationship between microbiota and disease symptoms offers important clues for innovative approaches to treatment.

Table 1. Microbiota changes and possible mechanisms observed in different psychiatric disorders

Psychiatric Disorders	Microbial Alterations	Bacteria	Mechanisms
Depression	Decreased diversity (alpha diversity ↓), pro-inflammatory bacteria ↑, SCFA-producing bacteria ↓	↓ Faecalibacterium, Coprococcus, ↑ Eggerthella, Bacteroides	Inflammation ↑, butyrate ↓, HPA axis disruption
Anxiety Disorder	SCFA ↓, Lactobacillus in some species ↑, decreased diversity	↓ Faecalibacterium, ↑ Lactobacillus	GABA metabolism, inflammation, vagal transmission disruption
Autism Spectrum Disorders	Firmicutes ↑, Bacteroidetes ↓, sulfate-reducing bacteria ↑	↑ Desulfovibrio, Lactobacillus, ↓ Bacteroides	GI inflammation, neurodevelopmental effects, metabolite imbalances
Schizophrenia	Diversity ↓, increased pro-inflammatory species	↓ Faecalibacterium, ↑ Lactobacillus, Prevotella	Glutamate-GABA imbalance, neuroinflammation
Bipolar Disorder	Decreased SCFA-producing bacteria, increased mucus-degrading species	↓ Faecalibacterium, ↑ Akkermansia	Inflammation ↑, intestinal permeability ↑
Post-Traumatic Stress Disorder	Beneficial bacteria ↓, pro-inflammatory species ↑	↓ Faecalibacterium, ↑ Actinobacteria	Effect of chronic stress on microbiota, HPA axis disruption

Bipolar Disorder

Microbial Changes

Bipolar disorder is a mood disorder characterized by cyclical episodes of depression alternating with mania or hypomania. While research on the microbiota in bipolar disorder is still in its early stages, existing evidence suggests parallels with depression and schizophrenia (Nikolova et al. 2021). A comprehensive review in 2022 reported only seven published studies on this topic; most of these included small sample sizes, potentially limiting consistency. However, most of these studies found that the composition of the gut microbiota in bipolar patients differed significantly from healthy controls. A common observation is a decrease in SCFA-producing bacteria such as Faecalibacterium, similar to those seen in depression (McGuinness et al. 2022). Additionally, some studies have reported an increase in Akkermansia, a genus associated with metabolism and intestinal barrier function, in bipolar patients (Painold et al. 2019).

Mechanisms

Findings related to the microbiota in bipolar disorder are consistent with the broader literature on inflammation and metabolic dysregulation in this population. In particular, there is evidence supporting chronic low-grade inflammation and increased intestinal permeability in bipolar disorder. A decrease in SCFA-producing bacteria may exacerbate inflammation by disrupting intestinal barrier integrity. Furthermore, an increase in Akkermansia may reflect altered mucosal metabolism or compensatory intestinal responses, but its precise role remains to be determined.

Preclinical Evidence

Unlike depression or schizophrenia, there are currently no robust preclinical (animal model) studies specifically investigating the effects of the bipolar-associated microbiota on behavior or neurobiology. This represents a significant gap in the literature and highlights the novelty of the field. Future preclinical studies examining fecal microbiota transplantation (FMT) from bipolar patients to germ-free animals may offer causal insights similar to those seen in schizophrenia research.

Clinical Evidence

A major study investigated the effect of probiotics on hospital readmission rates following acute manic episodes. In this randomized controlled trial, patients received either a probiotic supplement (containing *Lactobacillus* and *Bifidobacterium*) or a placebo for 24 weeks after hospital discharge. At six-month follow-up, the probiotic group had significantly lower readmission rates compared to the placebo group (Dickerson et al. 2018). This effect was particularly pronounced in individuals with elevated inflammatory markers, suggesting that microbiota-targeted interventions may exert protective effects by regulating inflammation. While replication is needed, these findings provide initial clinical support for microbiota modulation in bipolar disorder.

Bidirectional Effects

As with other psychiatric conditions, the relationship between the microbiota and bipolar disorder appears to be bidirectional. Individuals with bipolar disorder often exhibit poor dietary habits, metabolic syndrome, and psychotropic medication use, all of which can affect gut microbial composition. These lifestyle and pharmacological factors may obscure the direct relationship between the microbiota and the disease itself. Nevertheless, preliminary evidence suggests that the gut-brain axis may play a role in the pathophysiology of bipolar disorder, and this field is expected to expand in the coming years.

Post-Traumatic Stress Disorder

Microbial Alterations

Research on the relationship between post-traumatic stress disorder (PTSD) and the gut microbiota is relatively new. Preliminary human studies suggest that individuals with PTSD may have a different gut microbial profile compared to healthy controls. For example, one study reported an increase in the Actinobacteria phylum and a decrease in beneficial genera such as *Faecalibacterium* in individuals with PTSD (Bajaj et al. 2019). These findings suggest a dysbiotic microbial signature in trauma-exposed populations.

Mechanisms

PTSD is closely linked to chronic inflammation and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, both of which are known to interact with the gut microbiota. The microbiota has the capacity to regulate systemic and neuroinflammatory responses and influence the HPA axis. Therefore, microbial disturbances may exacerbate PTSD symptoms by affecting these key biological systems (Malan-Müller et al. 2018).

Preclinical Evidence

Animal models provide supporting evidence for the effects of trauma and chronic stress on the gut microbiota. In a study by Bharwani et al. (2016), chronic stress disrupted the gut microbial balance in mice, leading to increased anxiety-like behaviors. These findings suggest that gut dysbiosis may be both a consequence and a driver of trauma-induced behavioral changes.

Clinical Evidence

While comprehensive, large-scale studies in PTSD populations are not yet available, pilot studies in trauma-exposed groups (e.g., war veterans, disaster victims) have reported changes in microbiota composition. These studies suggest that microbiota changes may be associated with PTSD symptom severity and inflammatory markers (Malan-Müller et al. 2018, Bajaj et al. 2019). Increases in inflammatory biomarkers frequently observed in PTSD may be linked to microbial dysbiosis, supporting a possible inflammatory-microbial pathway in the pathophysiology of the disorder.

Bidirectional Effects

The relationship between PTSD and the gut microbiota is likely bidirectional. Trauma and chronic stress

can cause changes in nutrition, sleep, and gut motility, which in turn affect the microbiome, while the resulting dysbiosis can further impact emotional and cognitive symptoms through immune, endocrine, and neural pathways. This interplay suggests that the gut-brain axis may play a significant role in the maintenance and exacerbation of PTSD symptoms (Malan-Müller et al. 2018).

All these findings suggest that the relationship between the microbiota and psychiatric disorders is disorder-specific but shares some common mechanisms. They are summarized the microbiota changes and associated mechanisms across different disorders in Table 1.

Intervention Studies on the Effect of Microbiota on Mental Health

As evidence of the link between microbiota and mental health has begun to grow, attempts to use this relationship for therapeutic purposes have also come to the fore. The term “psychobiotic” was first introduced in 2013 by Dinan and colleagues to describe living organisms (probiotics) or supplements that can have beneficial effects on psychiatric diseases (Dinan et al. 2013). Since then, various interventions such as probiotics, prebiotics, dietary changes, and even fecal microbiota transplantation have been investigated for their effects on depression, anxiety, and other mental disorders. In this section, the effectiveness of these interventions will be evaluated in light of both clinical studies (human trials) and preclinical studies (animal models).

Probiotic Applications

Probiotics are supplements that generally contain beneficial bacteria for the gut, which when taken in sufficient amounts, benefit the host health. The most common prebiotics include inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS). These substances may reduce inflammation and regulate the gut-brain axis by promoting the growth of beneficial bacteria (e.g., *Bifidobacterium* and *Faecalibacterium* spp.), particularly those that produce butyrate (Slavin 2013, Louis et al. 2014, Gibson et al. 2017). In animal models, prebiotic supplementation has been observed to reduce anxiety-like behaviors and corticosterone levels (Burokas et al. 2017). The same study reported that the combination of FOS and GOS had positive effects on brain plasticity and BDNF levels. Although human studies are still limited, a pilot study has shown that FOS supplementation reduces stress levels and improves attentional processes (Schmidt et al. 2015). The effect of prebiotics is not limited to increasing microbial diversity alone; They may also have an impact on mental health by strengthening intestinal barrier function, regulating immune responses, and indirectly influencing neurotransmitter production. In this respect, they stand out as potential supportive agents with a more stable and less side-effect profile compared to probiotics. Many small-scale RCTs (randomized controlled trials) and pilot studies examining the use of probiotics in disorders such as depression and anxiety have provided evidence that probiotics may have positive effects on mood and anxiety levels. For example, a placebo-controlled study found that patients with major depression who were given a probiotic mixture containing *Lactobacillus acidophilus*, *L. casei*, and *Bifidobacterium bifidum* for 8 weeks had a significant decrease in depression scores compared to those who received a placebo (Akkasheh et al. 2016). Similarly, consumption of fermented foods and probiotics has been reported to reduce anxiety symptoms in healthy young adults with high anxiety scores (Hilimire et al. 2015). However, not all studies show consistent results; some RCTs have also suggested that probiotics alone have no significant effect. For example, there are studies that have difficulty showing the difference between probiotic use and placebo in healthy volunteers (Mohr et al. 2020). Therefore, it is understood that factors such as under what conditions, which strains, at what dose and for what duration are given are critical in order to reveal the effect of probiotics.

Nevertheless, meta-analyses in recent years have shown promising results when looking at the general picture. For example, a comprehensive umbrella meta-analysis published in 2022 reported that probiotics significantly alleviated depression symptoms when administered for more than 8 weeks and at high doses (at least 10 billion live bacteria per day) (Musazadeh et al. 2023). In this analysis, it was emphasized that the effect of short-term or low-dose probiotic use was not clear and that sufficient time and dose were required for the effect to occur. It is also suggested that multi-species probiotic combinations are

generally more successful than a single species (as they may provide a wider range of mechanisms of action).

Studies are also ongoing on which probiotic strains are more effective. The most commonly used psychobiotic strains in the literature include the genera *Lactobacillus* (especially *L. rhamnosus*, *L. helveticus*, *L. casei*) and *Bifidobacterium* (*B. longum*, *B. bifidum*, *B. infantis*, etc.). Most of these bacteria are selected due to their potential to affect GABA or serotonin metabolism, reduce inflammation, or regulate HPA axis response (Bravo et al. 2011, Yong et al. 2020). For example, *Bifidobacterium longum* 1714 strain has been shown to reduce stress-induced memory impairments and improve sleep quality in humans (Allen et al. 2016). A study reported that the combination of *Lactobacillus helveticus* R0052 and *B. longum* R0175 reduced anxiety and depression scores and balanced cortisol levels (Messaoudi et al. 2011). Such findings suggest that different probiotics may contribute to mental health with different mechanisms of action.

Dietary Adjustments (Role of Diet)

Another way to modulate the microbiota is to change the diet. Diet is one of the most important determinants of the composition of the gut microbiota; therefore, adopting a healthy dietary pattern may benefit mental health via the microbiota. This hypothesis was tested in the late 2010s with diet randomized controlled trials. One of the most well-known studies is an RCT conducted in Australia known as the SMILES study (Jacka et al. 2017). 67 patients diagnosed with major depression were assigned to one of two groups for 12 weeks: One group followed a Mediterranean-style diet program with a dietitian, while the other group attended regular social support meetings but did not receive a special diet. At the end of the 12 weeks, 32% of the patients in the dietary intervention group were in complete remission (disappearance of depression symptoms), while only 8% in the control group were in remission. The mean improvement in depression scores in the diet group was also significantly greater than in the control group. This striking result has proven for the first time in a controlled trial that healthy nutrition can help treat depression. A similar study, the HELFIMED trial, provided fish oil supplementation in addition to the Mediterranean diet and again observed a significant improvement in depression symptoms (Parletta et al. 2019). The common characteristics of the Mediterranean diet – high fiber, a variety of vegetables and fruits, whole grains, legumes, fish, olive oil and fermented dairy products; low red meat and processed foods – are also extremely positive for the gut microbiota. This diet has been shown to increase butyrate-producing bacteria in the gut, suppress inflammation and reduce circulating LPS levels (Seethaler et al. 2022). Therefore, the possible effects of dietary adjustment are mediated by the microbiota.

In patients with depression who follow the Mediterranean diet, beneficial microbiota profiles (e.g. high *Faecalibacterium* levels) have been noted to return and this has been correlated with depression improvement in small studies (Jacka et al. 2017). Not only the Mediterranean diet, but also some other specific dietary patterns such as ketogenic diet and vegan diet are being studied in neuropsychiatric conditions. For example, there are case reports that ketogenic diet may be beneficial in bipolar disorder by reducing inflammation (Phelps et al. 2013); it is thought that some of this effect may be related to the effects of ketogenic diet on microbiota (ketogenic diet has beneficially altered gut microbiota in some epilepsy models). However, large-scale RCTs of such special diets have not yet been conducted. In general, dietary approaches are low-risk strategies that can provide multidimensional benefits in terms of mental health. A diet that makes the microbiota conducive to health (provides eubiosis) is seen as a holistic treatment method, as it can improve not only psychiatric symptoms but also accompanying physical problems (e.g. obesity, metabolic syndrome). Of course, diet should not be considered as a “treatment” alone in severe psychiatric disorders; However, it is gaining value as a complementary treatment that can be applied in addition to standard treatments and strengthen the results.

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) is a treatment method based on the principle of transferring gut microbiota obtained from healthy individuals to patients. Initially used with high success in the treatment

of antibiotic-resistant *Clostridium difficile* infections (Kelly et al. 2016, Settanni et al. 2021), FMT has recently begun to be investigated for the treatment of psychiatric disorders. Experiments in which microbiota from patients diagnosed with depression and anxiety disorders were transferred to healthy animal models have shown that the recipient animals exhibited depression- and anxiety-like behaviors (Zheng et al. 2016, Kelly et al. 2016, Settanni et al. 2021). At the clinical level, a study conducted in children with autism spectrum disorder observed significant improvement in gastrointestinal symptoms and accompanying behavioral improvements after 8 weeks of FMT (Kang et al. 2017). However, there is not yet sufficient evidence on the effectiveness and reliability of FMT in psychiatric disorders, and more comprehensive and controlled clinical studies are needed in the future (Vendrik et al. 2020, Settanni et al. 2021).

Future Directions and Implications for Clinical Practice

As the scientific understanding of the interactions between microbiota and mental health deepens, the potential to translate this knowledge into clinical practice also comes to the fore. There are various predictions about how microbiota-based approaches in psychiatry may take shape in the coming years. This section will discuss personalized psychobiotic treatments, the development of microbiota-based biomarkers, and the potential for translational research to be reflected in clinical practice.

Personalized Psychobiotic Treatments

An important future direction will be to develop personalized microbiota modulation strategies. Our current knowledge shows that everyone's microbiota is unique like a fingerprint and that a "one size fits all" probiotic approach would be too simplistic (Goldiş et al. 2025). Therefore, in the future, the most appropriate intervention will be determined by taking into account each individual's microbial composition and mental state. For example, a depressed patient with very low levels of certain beneficial bacteria may be offered a special probiotic formulation containing exactly those deficient bacteria. Or, in a patient with significant anxiety, a combination of both probiotics and prebiotics that will increase GABA-producing bacteria can be designed specifically for the individual (Gibbons et al. 2022). To achieve this, the patient's gut microbiota profile should first be analyzed in detail (with methods such as metagenomic sequencing and metabolomic analysis). Then, imbalances that can be corrected in that profile are targeted based on the data. This approach can provide higher success than fixed-content probiotic supplements that appeal to the general population (Chiu and Miller 2019).

Personalization can be done not only according to the microbiota profile, but also according to the clinical characteristics of the patient. For example, in a depressed patient with high inflammation, psychobiotics known for their anti-inflammatory effects (e.g. *Bifidobacterium longum*) may be preferred, while in another with predominant sleep problems, a dietary supplement or probiotic that affects melatonin metabolism may be selected (Pinto-Sanchez et al. 2017). Similarly, a different microbial approach targeting the regulation of glutamate metabolism in a patient with obsessive-compulsive disorder could be considered. Besides, microbiota composition is profoundly influenced by geographic, ethnic, and cultural differences. For example, Asian diets are higher in fiber intake, while Western diets contain more fat and sugar, radically altering the bacterial profile (Yatsunen et al. 2012).

Therefore, direct generalization of US or European microbiota findings to Mediterranean cultures like Türkiye or developing countries may pose a methodological challenge. Therefore, increased regional studies and culturally sensitive analyses are recommended. Although such a precision psychiatry approach is still a vision on the horizon, it may become more tangible when supported by microbiome science. Indeed, the concept of "microbiome-guided therapy" has already taken its place in the literature (Meneses do Rêgo and Araújo-Filho 2025). The idea of increasing the effectiveness of pharmacotherapy with microbiota-based adjuvant treatments (e.g. specific probiotics), especially in treatment-resistant cases, is gaining traction. Personalized psychobiotic therapy requires holistic assessment of microbiota analysis, symptom severity, lifestyle, and cultural factors. A potential clinical workflow outlining this process is presented below (Figure 1).

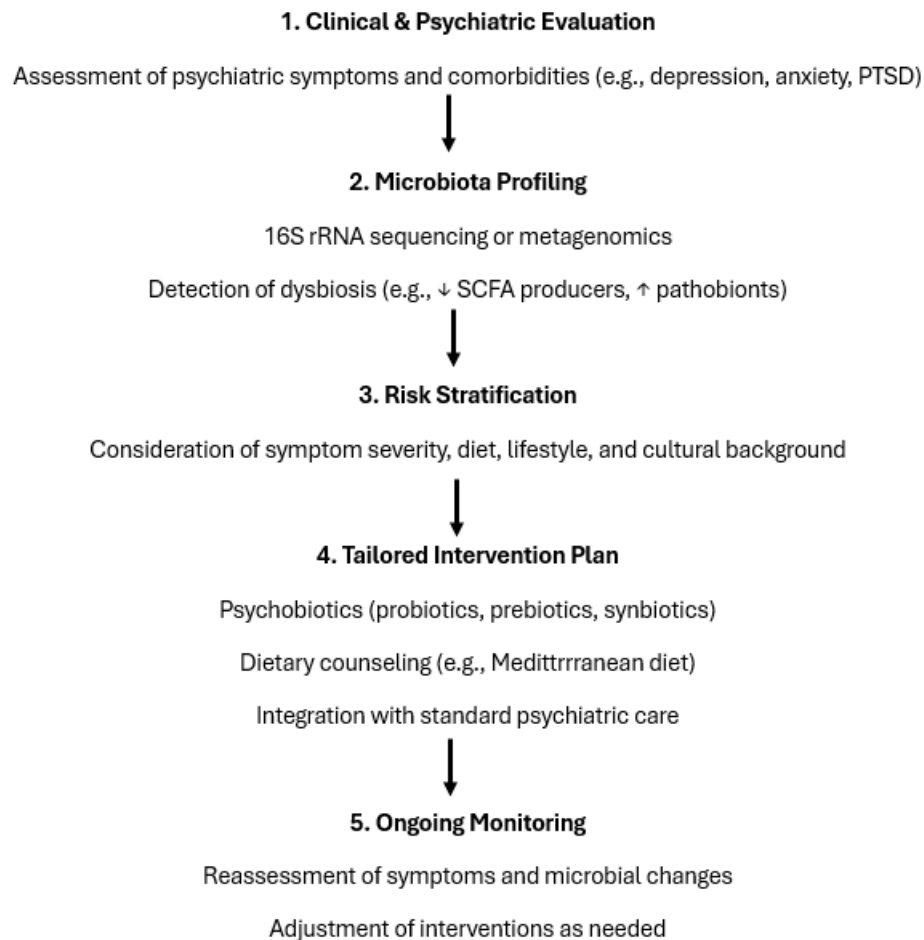


Figure 1. Clinical workflow for personalized psychobiotic therapy

Microbiota-Based Biomarkers

Another important area for the future is the development of microbiota-based biomarkers. The lack of objective biomarkers in psychiatric disorders has long been a problem. Diagnoses are still based on subjective symptom assessments, which can lead to both late diagnoses and uncertainties in mixed presentations (Nikolova et al. 2021). Microbiome research can open a new window in this area. For example, if a certain change in the gut microbiota can be detected before a diagnosis of depression is made, this can be used as an early warning sign. Or, if it can be predicted which antidepressant a patient will respond better to by looking at their microbial profile, treatment can be planned specifically for the individual (Radjabzadeh et al. 2022).

Some studies are currently being conducted in this direction. For example, Jiang et al. (2015) suggested that an increase in *Enterococcus* and *proteobacteria* in the microbiota of individuals diagnosed with depression for the first time may be associated with a poor response to selective serotonin reuptake inhibitors (SSRI) antidepressants. If similar findings are confirmed, in the future, it will be possible to look at the patient's stool analysis and say, "your gut profile does not currently resemble the group that responds well to medication, let's improve the microbiota first." On the other hand, certain bacterial metabolites are also candidates for biomarkers. For example, butyrate or propionate levels in the blood, or a microbiota-derived molecule in the urine (such as indole-propionic acid) may be a signature reflecting the risk of depression. Clues can even be caught by looking at the stool cocktail: For example, a recently published artificial intelligence study presented a machine learning model that can distinguish individuals with depression based on stool microbial structure with over 80% accuracy (Averina et al. 2024). As such approaches develop, a "psychiatric microbiome panel" can be designed as a laboratory panel. Microbiota-

based markers can be used not only for diagnosis but also for monitoring treatment targets. For example, if a probiotic is given during treatment and we want to understand whether it has really settled in the patient's microbiota, this can be followed with a simple stool test. Or, microbiota analysis can be performed to predict the risk of side effects of a drug (the weight gain effect of some antipsychotics may be mediated by intestinal bacteria; if this can be predicted, patients at risk can be identified in advance) (Theriot et al. 2022). Of course, in order for a biomarker to enter clinical use, its reliability and validity studies must first be carried out meticulously. Since the microbiota is a dynamic system, a measurement can change over time and conditions. Therefore, it is difficult to determine repeatable and specific parameters. However, it is thought that combined parameters (for example, scores that evaluate multiple bacterial ratios or metabolite levels together) may be more stable. Large databases such as "PsycGM" are created to compile which microbial characteristics have the strongest relationships with which disorders (Delanote et al. 2024).

Translational Research and Clinical Applications

Translational research needs to be strengthened in order to translate microbiota and mental health knowledge into clinical practice. Translational research refers to the process of testing basic science findings on humans and translating them into applicable interventions (Gebrayel et al. 2022). There are several important focal points in this area:

1. **Large-scale, well-designed clinical trials:** More comprehensive RCTs are needed to evaluate the effectiveness of interventions such as probiotics, prebiotics, diet, and FMT. Sample sizes large enough to perform subgroup analyses, especially in heterogeneous patient groups, should be targeted. For example, a multicenter probiotic trial of 300-500 people in depression would help the field reach reliable evidence. Some probiotic companies and independent consortia are currently planning such studies. In the future, successful interventions may be licensed and included in guidelines (Huang, Wang and Hu 2016).
2. **Pharmacobiotic interactions:** The interactions between drugs currently used in psychiatry and the microbiota need to be better understood. It is known that most antidepressants and antipsychotics directly affect the gut microbiota (e.g., some antidepressants also have antibacterial effects). This suggests that, on the one hand, drugs have some effects through the microbiota, and on the other hand, microbiota changes may modulate the effectiveness or side effects of the drug (Meneses do Rêgo and Araújo-Filho 2025). In the future, before starting a certain drug, the patient's microbiome can be analyzed to see if there is a microbial factor that may prevent the drug from working in that person. This can guide drug selection. For example, if a gut bacterium that reduces the effect of SSRIs is detected, treatment can be given together with a method that suppresses that bacterium (diet or probiotics). Such microbiome-guided pharmacotherapy studies are just beginning to come to the fore (Yaqub et al. 2025).
3. **Microbiota-diet-psychosocial interactions:** Since mental health is a complex area, multi-component approaches rather than a single intervention will gain importance in the future. For example, for a patient with depression, a combination of psychotherapy, exercise, diet and probiotics may be the most effective. The synergistic effects of such combinations should be investigated. Initial indications are that a healthy diet and probiotic intake may have a stronger effect together (e.g., a fiber-rich diet may increase the effectiveness of probiotics). In addition, "integrated treatment" models that address both mental and physical health in a holistic manner can be developed, taking into account individual factors that moderate the microbiota-diet axis (e.g., food intolerances, intestinal inflammatory conditions) (Berding et al. 2022, Sochacka et al. 2024).
4. **Public health and preventive medicine:** Increased knowledge about microbiota may also be reflected in strategies for protecting mental health. For example, supporting the development of healthy microbiota during infancy (encouraging normal birth, increasing breast milk intake, limiting unnecessary antibiotic use) can be seen as an investment in the mental health of the

society in the long term. Some studies suggest that the development of microbiota in the first 1000 days of life affects the child's brain development. In light of this information, pediatric and obstetric practices can be reviewed. Again, healthy nutrition campaigns can be emphasized to prevent not only physical diseases but also common disorders such as depression (Pantazi et al. 2023).

Conclusion

The findings presented in this review demonstrate that the relationship between gut microbiota and mental health is increasingly well-founded. Long overlooked, the microbiota is now recognized as a significant biological factor in the field of psychiatry, with its impact on our brain and behavior. Research conducted over the past decade has shown that microbial balance is disrupted in depression, anxiety, autism, schizophrenia, and other psychiatric disorders, and that this disruption can affect brain function through mechanisms such as inflammation, neurotransmitter production, and the HPA axis. Studies on the microbiota-mental health axis are rapidly increasing, and findings, particularly in the field of depression and anxiety, are approaching clinical practice. However, interindividual variability of the microbiome, methodological differences, and uncertainties regarding causality are among the fundamental limitations of this field. However, more advanced research designs and technological innovations have the potential to overcome these obstacles.

The importance of integrated approaches to mental health is one of the key takeaways from this review. The human body and mind should be considered as a whole; gut-brain axis is a key indicator of this integrity. In this context, it is crucial that psychiatric treatments be structured as multimodal interventions that target not only the brain but also gut health. In addition to antidepressant treatment, the combined use of interventions such as probiotics, psychotherapy, and exercise can contribute to both mental and physical well-being. The microbiota-mental health relationship offers a new paradigm for psychiatric illnesses. This relationship enables assessment of illnesses not only from a brain-centered perspective but also at a systemic level. It also reduces stigma and facilitates patient engagement in treatment. The ability to modulate the microbiota through lifestyle changes supports individuals' active participation in the treatment process. In the summary, the relationship between microbiota and mental health has become one of the most dynamic research areas in modern medicine. Interdisciplinary collaborations are crucial for translating this relationship into clinical practice. As future studies prove the effectiveness of microbiota-based interventions, this approach is expected to become an integral part of mental health services.

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