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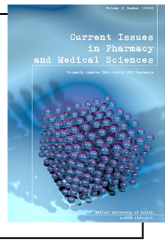


# The impact of gut microbiota on mental health

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**ABSTRACT**

Microorganisms inhabit various areas of the human body, but by far the most numerous and diverse in species is the intestinal microbiota. This consists of an enormous number of microorganisms, the largest group of which are bacteria. Currently it is well known that microbiota affects the proper functioning of the brain, therefore, it has become the subject of interest in the field of mental diseases treatment. Numerous studies have shown both quantitative and qualitative disturbances in the composition of the intestinal microbiome in people suffering from depression. Psychobiotics are a category of probiotics that influence the gut microbiota and positively impact brain and nervous system function. The potential antidepressant role of psychobiotics is also indicated, however, presently, they do not have the status of drugs. It is well known that they induce various beneficial effects, such as reducing the level of cortisol and the activity of the hypothalamic-pituitary-adrenal (HPA) axis, as well as modulating the activity of the vagus nerve. Furthermore, the studies conducted so far allow to confirm the relationship between the composition and abundance of intestinal microflora and occurrence of various mental diseases, including: depression, schizophrenia, bipolar disorder, autism and attention deficit hyperactivity disorder (ADHD).

## INTRODUCTION

The human intestinal microbiota is a complex community of microorganisms, including fungi, viruses, archaea and eukaryotes, with bacteria constituting the biggest group. It is the largest microsystem of the human body that enters into symbiosis with the host and allows physiological processes to be maintained in a dynamic state of balance [1]. Intestinal microbiota performs many useful functions in the body. It influences the proper functioning of the intestines, ensuring appropriate pH, intestinal peristalsis and regular bowel movements. It takes part in the digestion of food by secreting digestive enzymes and transforming complex nutrients into simple compounds. The intestinal microbiota is also responsible for synthesizing vitamins such as B and K and neutralizing toxins and carcinogenic compounds [2]. Furthermore, it creates an intestinal barrier preventing pathogens from entering the body [3] and stimulates the proper development and maturation of immune cells [4]. Therefore, any changes in the composition and amount of intestinal microbiota may adversely affect the health of the macro-organism. These transformations may be influenced by use of many commonly described drugs, including antibiotics, proton pump inhibitors and metformin, which may induce translocation or directly affect the growth of intestinal bacteria [5]. It is known that the microbiota is also influenced by diet, especially vegetarian, which increases the variability of the presented microbial species. It was also noticed that aging causes a decrease in microbiological diversity, while genetic factors significantly influence the number and species diversity of the intestinal microbiome and contribute to the variability of susceptibility to pathogens [6].

The gut microbiota is of great interest among researchers, especially due to its impact on mental health. The purpose of this review is to present the impact of the intestinal microbiota on diseases such as depression, schizophrenia, attention deficit hyperactivity disorder (ADHD), bipolar disorder and autism. The information contained in this review article was retrieved using the PubMed database. The selection was based on the keywords: “microbiota”, “microbiome”, “gut”, “microbiota brain-gut axis”, “depression”, “schizophrenia”, “bipolar disorder”, “autism”, “ADHD”.

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## Microbiota-brain-gut axis

The gut microbiota affects the host through neural, immunological, neuroendocrine and metabolic pathways, as reflected in the microbiota brain-gut axis [7]. It is bidirectional communication system between the gastrointestinal tract and the central nervous system. The vagus nerve is a direct connection between the intestines and the brain. Intestinal enteroendocrine cells can interact with vagal afferents by releasing serotonin or intestinal hormones. Furthermore, they also secrete Toll-like receptors (TLRs), which mediate the detection of the Gram-negative bacteria cell membrane component – lipopolysaccharide (LPS). This explains how the microbiota is able to sense the vagus nerve through direct mechanisms, including activation of the TLR4 receptor, which responds to LPS [8].

Disturbances in the microbiological composition of the intestines lead to an increase in the permeability of the intestinal barrier and the blood-brain barrier. As a result, increased intestinal permeability leads to a systemic inflammatory response. The movement of Gram-negative bacteria containing LPS may excessively activate the immune system, causing a significant rise in pro-inflammatory cytokines. Additionally, the microbiome likely regulates the differentiation and maturation of macrophages forming microglia, which play a key role in the development of cognitive functions and social behavior and influence immune functions.

Microbiota is also necessary for the proper functioning of the hypothalamic-pituitary-adrenal (HPA) axis because it directly affects the production of glucocorticosteroids and immunological mediators, including interleukins 1β and 6 or tumor necrosis factor (TNF-α), which in turn stimulates this axis. It is known that corticotropin-releasing hormone (CRF) secretion and stimulation of the HPA axis promote the development of mental diseases. CRF is a peptide that affects the production and release of adrenocorticotropic hormone (ACTH) in the pituitary gland and is thus the main mediator of the activation of the HPA axis response to stress. As a result of the ACTH effect, the adrenal glands release cortisol which modulates the secretion of cytokines acting on the HPA axis and thus affects the immune system and causes the differentiation of the intestinal microbiota [9]. Recent studies using animal models suggest that dysbiosis of intestinal microbiota may cause the development of mental disorders [7].

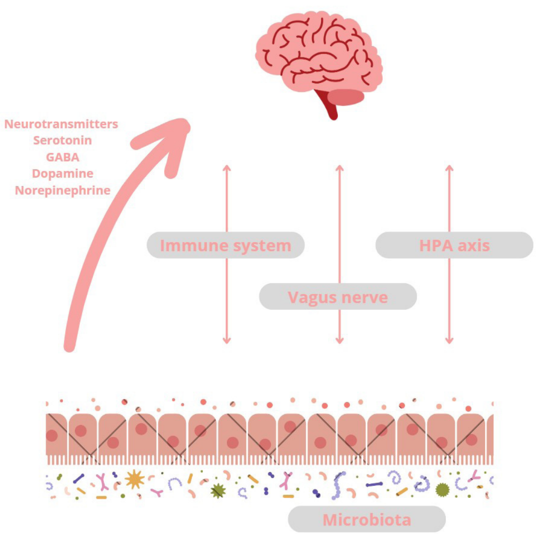


***Figure 1.*** Illustration of the microflora-gut-brain axis. The communication pathways between the gut microbiota and the brain include vagus nerve, hypothalamic-pituitary-adrenal (HPA) axis, immune system. Microbiota also affects the brain through the production of neurotransmitters (own elaboration)

## Depression

Depression is a significant mental disorder affecting an increasing number of individuals globally, often leading to tragic outcomes such as suicides. This condition is characterized by symptoms including low mood, changes in appetite, sleep disturbances, decreased energy, reduced concentration and a sense of worthlessness. The precise mechanism of depression remains still unknown but currently it is suggested that changes in neurotransmission, neuroplasticity, inflammation and stimulation of the HPA axis may contribute to this state [10, 11]. Treatment typically involves a combination of the administration of antidepressants and psychotherapy, with selective serotonin reuptake inhibitors (SSRI) as the most commonly prescribed drugs [12]. Recent research has explored the connection between alterations in the intestinal microbiota and depression. Consequently, it has been suggested that the use of psychobiotics which are probiotic bacteria that positively impact mental health when consumed, could become a promising alternative to conventional pharmacotherapy [10].

As mentioned earlier, changes in neurotransmission play a crucial role in the onset of depression. Excitatory neurotransmitters, including glutamate, acetylcholine and dopamine, as well as inhibitory neurotransmitters like γ-aminobutyric acid (GABA), glycine and serotonin, influence brain functions such as movement and emotions [13]. Previous studies have demonstrated that intestinal bacteria may produce various substances, including GABA (*Lactobacillus spp*., *Bifidobacterium spp*.), acetylcholine (*Lactobacillus spp*.), serotonin (*Escherichia spp*., *Candida spp*., *Enterococcus spp*.), dopamine (*Bacillus spp*.) and norepinephrine (*Bacillus spp., Saccharomyces spp*.). Furthermore, notably *Bifidobacterium infantis* influences the level and metabolism of tryptophan, a precursor of serotonin, indirectly contributing to increased serotonin concentration and potentially preventing depression. Serotonin, being a large molecule, is not able to cross the blood-brain barrier and enter the brain directly. The serotonin produced in the gastrointestinal tract performs local functions by regulating bowel movements. However, tryptophan can cross the blood-brain barrier, allowing for the synthesis of serotonin in the brain [2,7].

The serotonin hypothesis suggests that disturbances in serotonin levels contribute to the development of depression. This is most likely caused by a lower release of this neurotransmitter, an insufficient number of serotonin receptors, incorrect signal transmission through the serotonin receptor or a deficiency of the serotonin precursor - tryptophan. Behavioral studies have noted that administering *L. plantarum* to germ-free mice causes a significant increase in serotonin and dopamine. *Cl. ramosum* in the intestines also influences the increased production of serotonin. In addition, bacteria also have the ability to produce serotonin *in vitro*. The presence of this neurotransmitter was discovered in histidine decarboxylase broth containing *K. pneumoniae, H. alvei*, and *M. morganii* strains. Moreover, lactic acid bacteria such as *L. plantarum, L. cremoris, L. lactis* are known to produce serotonin in the arginine decarboxylase broth. There is also a catecholamine hypothesis suggesting that norepinephrine and dopamine deficiency contributes to depressed mood. For example, *B. mycoides* and *B. subtilis* have the ability to secrete norepinephrine. Indeed, significant levels of dopamine and norepinephrine were detected in the intestinal lumen of germ-free mice harboring *Clostridium* species. *E. coli* bacteria can also produce serotonin and dopamine in the culture medium. Additionally, strains of *P. vulgaris, S. aureus*, and *S. marcescens* are producers of dopamine. Whereas *B. mycoides* and *B. subtilis* have the ability to secrete norepinephrine [7].

Furthermore, inflammation is believed to heighten susceptibility to depression [14], triggered by immune system activation, and dysregulation of immune cells and mechanisms may contribute to mental disorders. Additionally, microbiota metabolites, such as Short-Chain Fatty Acids (SCFAs) like acetate, butyrate and propionate, are involved in anti-inflammatory processes. Scientific research suggests that these compounds may have promising benefits related to pain, depression and neurodegenerative diseases. SCFAs interact with NLRP3 inflammatory cells, enhancing interleukin-8 (IL-8) production and improving intestinal barrier tightness. Moreover, SCFAs influence immune cells by inhibiting the formation and differentiation of dendritic cells, crucial for immune functions. Butyrate and propionate, in particular, demonstrate the potential to regulate immune functions and maintain the integrity of the blood-brain barrier. Butyrate, as a byproduct of intestinal bacteria metabolism, modulates neurotransmitter synthesis, affecting the nervous system [10].

In the study by Liu *et al.,* the intestinal microflora of 43 people with depression was compared with 47 healthy people. Differences between the subjects were demonstrated. People with depression had higher levels of *Bacteroides* and lower amounts of *Firmicutes*. They also had lower levels of *Faecalibacterium* and members of the *Ruminococcaceae* family. The authors of the study concluded that these changes led to a reduction in the ability to produce SCFAs in people with depression [15]. Similarly, in the study conducted by Huang and colleagues a significant decrease in the number of *Firmicutes* was observed in stool samples of people with depression [16]. Based on these studies, it can be concluded that reducing the number of *Firmicutes* reduces SCFA. It is believed that disturbances in SCFA levels weaken the intestinal barrier, the leakage of which allows pathogens and their metabolites to cross it. This induces an immune response influencing the development of depression. In summary, the impact of SCFAs in the intestinal microbiota appears to play a significant role in inflammatory processes, pain management, immune capacity and neurological functions what highlighting its potential in mental and physical health research [10].

### Autism

Autism spectrum disorder (ASD) is a comprehensive set of neurobehavioral disorders characterized by restricted and repetitive behavior, impaired social interaction and communication. In view of lack of effective therapy for this disease, research on the role of intestinal microorganisms is becoming more and more advanced. Such research employs a variety of approaches. On comparing the composition of the intestinal microbiota between samples of autistic children and the control group, it was found that autistic children are characterized by a greater number of species of the *Clostridium* genus, and their microbiota composition shows an imbalance between the *Bacteroidetes* and *Firmicutes* phyla. In particular, there is an increased presence of Bacteroidetes and other commensal bacteria such as Bifidobacterium, Lactobacillus, Sutterella, Prevotella, Ruminococcus genera and the Alcaligenaceae family. It has been suggested that a change in bacterial composition may lead to the production of neurotoxins, contributing to autistic symptoms. This notion has been confirmed by different research. Still, the existence of intestinal dysbiosis as an etiological factor of ASD is controversial [17]. It was also noticed that symptoms of autism appeared after the use of antibiotics, and the administration of oral vancomycin alleviated these symptoms. Additionally, improvement in autistic symptoms was observed in two children after fecal microbiota transplantation [18]. Therefore, this method of treatment may prove to be a way to combat this disorder in the future. Although ASD is one of the most important and serious neurodevelopmental diseases, there is a need for further research to thoroughly understand the relationship between the microbiota and ASD.

### Schizophrenia

Schizophrenia is a serious mental disorder characterized by positive, negative and cognitive symptoms such as hallucinations, delusions and social withdrawal. Various sources indicate that it affects approximately 1% of the world's population and generates significant health care costs [19]. The pathomechanism of schizophrenia is not fully explained due to a number of potential factors that may influence the development of this disease. One concept assumes the involvement of the dopaminergic and glutamatergic systems. It is known that an increase in dopaminergic transmission in the mesolimbic part and inhibition of glutamatergic transmission are associated with the occurrence of positive symptoms of schizophrenia [20]. Furthermore, there is also a growing body of evidence that immune dysfunction is a key element of its pathogenesis. Recently, there has been an increasing amount of data indicating a close connection between infections or immunological disorders and the development of schizophrenia. Additionally, it has been observed that anti-inflammatory medications may provide relief of schizophrenia symptoms [2]. Most likely, changes in the intestinal microbiota may also lead to systemic inflammation and thus contribute to its development. Recent research suggests that inflammation may lead to activation of microglia and the kynurenine pathway, which in turn may activate systemic schizophrenic symptoms. Further research is needed to explore the mechanisms that underlie the relationship between inflammation and the microbiota brain-gut axis and to understand its association with this disease. However, a high risk of schizophrenia may also be linked to genetically increased levels of serotonin. The family *Enterobacteriaceae* and the order *Enterobacteriales* can produce SCFAs, such as acetic acid and formic acid, through carbohydrate fermentation. This process, may stimulate serotonin biosynthesis by enterochromaffin cells, the main source of this neurotransmitter, which consequently increases the risk of schizophrenia. Also, the *Enterobacteriales* family and the *Gammaproteobacteria* class are important biomarkers of schizophrenia, as evidenced by cross-sectional studies [21]. Patients with schizophrenia have lower levels of bacteria from the *Proteobacteria* phylum, higher levels of the *Anaerococcus* genus and lower levels of *Haemophilus spp., Sutterella spp*. and *Clostridium spp*. bacteria compared to the healthy control group. In addition, these patients have an abundance of *Ruminococcaceae*, which is associated with milder negative symptoms, and *Bacteroides*, which is associated with more severe depressive symptoms [22].

### Bipolar disorder

Bipolar disorder (BD) is a recurrent and chronic mental illness characterized by disturbances in mood and energy. It affects over 1% of the world's population and is one of the main causes of disability among young people, leading to increased mortality, especially as a result of suicide. It includes two mental states: depression and mania. People experiencing a depressive episode will experience low mood, hopelessness, deep sadness and lack of interest in life. However, people in a manic state will experience elevated mood, increased activity, rapid thinking and a limited need for sleep [23]. BD is an inherited disorder, the development of which is influenced by genetic and environmental interactions. Imbalance in monoaminergic systems, such as the serotonergic, dopaminergic and noradrenergic neurotransmitters plays an important role in the disorder. Research also indicates the involvement of inflammatory processes in the development of this disease, as increased activity of peripheral inflammatory cytokines is observed, including high concentrations of IL-6, TNFα and C-reactive protein (CRP). Herein, it has been found that CRP levels increase during a manic episode.

Microbial metabolites such as LPS, which is the main component of the outer cell membrane of Gram-negative bacteria, may cause immune reactions by breaking the gastrointestinal barrier and entering the general circulation, and an altered microbiological profile is observed in patients with bipolar disorder. Studies indicate that patients with bipolar disorder have reduced numbers of *Firmicutes* and *Faecalibacterium spp*. compared to healthy controls. However, probiotic intervention containing *Lactobacillus spp*. and *Bifidobacterium lactis* strains reduces the number of hospitalizations in people who have previously experienced manic episodes [20]. New research has provided preliminary evidence that a marker of inflammatory bowel disease, anti-Saccharomyces cerevisiae antibodies (ASCA), is elevated in BD. These results suggest an important role of the gastrointestinal tract in the pathology of bipolar disorder. There is also the concept of antibiomania, which means the occurrence of a manic episode caused by antibiotics. This is a rare but important side effect of many antibiotics taken by BD patients during bacterial infections. However, the mechanism of action and its relationship to the onset of mania remain unclear. The occurrence of long-lasting or intense psychiatric symptoms following antibiotic use may provide specific data on the role of two-way communication between the microbiome and the brain [24].

### ADHD

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder that manifests itself through three main features: inattention, impulsivity and hyperactivity. Without proper therapeutic treatment, ADHD may result in serious consequences, such as learning difficulties, problems in social relationships, cases of unwanted accidents, tensions in family relationships and disruption of a professional career [25]. The etiology of this disorder is multifactorial, and particular emphasis is placed on genetic factors. It is suggested that a key element of the pathophysiology of ADHD may be impaired functioning of catecholaminergic neurotransmission [26]. Increasingly, the occurrence of ADHD is associated with disorders on the microbiota-brain-gut axis. It is known that dysbiosis causes oxidative stress, the increased level of which is observed in the course of ADHD. Additionally, microbiota study in patients with this disorder conducted by Aarts *et al*. showed that the *Actinobacteria* phylum (including *Bifidobacterium*) was more abundant, while the number of *Firmicutes* decreased. The same study showed that the microbiome of people with ADHD has an increased ability to produce cyclohexadienyl dehydratase (CDT), which participates in the synthesis of the dopamine precursor, phenylalanine [27]. In another study a decrease in the number of bacteria of the *Faecalibacterium* genus (*Ruminococcaceae* family) and an increase in the concentration of *Odoribacter* (*Bacteroidales* order) and *Enterococcus* were observed [2]. It is also worth noting the connection between the concentration of omega-3 fatty acids and the intestinal microbiome in patients with ADHD. In general, total omega-3 fatty acids concentrations are significantly reduced in pediatric patients with this disorder. In animal studies, a significant increase in the *Firmicutes*: *Bacteroidetes* ratio was observed in mice consuming a diet low in these acids, while at the genus level, mice consuming a rich diet showed a significant increase in *Lactobacillus* and *Bifidobacterium* in adulthood. Currently, omega-3 fatty acids are enjoying great interest since they can be an alternative or complementary therapy in the treatment of ADHD and have a beneficial effect on the intestinal microbiota [26].

### Psychobiotics and mental disorders

The role of diet in the formation of the human intestinal microbiota is a key factor from early childhood to old age. Therefore, dietary interventions have the potential to modify psychological symptoms associated with gut-brain dysfunction [28]. Diet directly impacts the gut microbiota. It is important for food to contain a variety of ingredients such as vegetables, fruits and unprocessed products that support the growth of beneficial bacteria. A monotonous diet, consisting mainly of highly processed products and sweets and low in fiber, can cause dysbiosis, which is an imbalance between commensal and pathogenic bacteria. The proliferation of *Lactobacillus* and *Bifidobacterium* bacteria, which are crucial for maintaining microbiome balance and human health, requires the consumption of plant-based proteins [29]. Probiotics are preparations or food products containing strains of live microorganisms. They are commonly employed especially during antibiotic therapy, to prevent intestinal dysbiosis. Psychobiotics are a group of probiotics that act on the intestinal microflora and have a beneficial effect on the functioning of the brain and nervous system. The strains of microorganisms incorporated in the preparation of these products have proven effects that support neurodevelopment and help regulate mood. Psychobiotics include both live microorganisms and their metabolites, which have positive health effects on the body of patients with mental illnesses. Among the bacterial strains, the exploitation of which brings beneficial health effects, we can distinguish: *Streptococci, Enterococci, Lactobacilli, Bifidobacteria* and *Escherichia* [30]. The mechanism of action of psychobiotics is the production of neurotransmitters, SCFAs, enteroendocrine hormones and anti-inflammatory cytokines.

Numerous studies have shown that the ingestion of these agents is effective in the treatment of anxiety or depression and more advanced neuropsychiatric diseases. It is worth emphasizing that all psychobiotics are probiotic preparations, but not all probiotics are psychobiotics. Probiotic products are in high demand and their market demand is increasing due to the health benefits resulting from their use. Psychobiotics are also increasingly becoming available on the market. However, research is still needed to determine the beneficial properties of specific strains, as well as the safety of their use. However, they have great potential to be employed as agents in mild forms of depression or anxiety, as well as as adjuvants in the therapy of more advanced diseases of the central nervous system [31].

## CONCLUSIONS

Research on the intestinal microbiota is an interesting area of science that has great potential for further discoveries, especially in terms of understanding the exact mechanisms and interactions between intestinal microorganisms and the central nervous system. The progressive development of modern technologies has allowed us to discover the relationship between changes in the microbiological composition of the intestines and their impact on mental health. The results are encouraging, but further research is needed to draw more specific conclusions, especially with human participation. Table 1 presents an overview of the studies reporting the effects of various bacteria strains on mental health. It is known that intestinal dysbiosis and any imbalances in the microbial composition due to the intestinal-central nervous system connection adversely affect the mental health of the host. Therefore, it is important to care for a healthy intestine by eating a nutritious diet or supplementing the intestinal microbiotic composition by incorporating in the diet preparations containing strains with proven health benefits. Diseases related to the human psyche, especially depression, which affects an increasing number of people every year, require new therapeutic approaches to alleviate both the symptoms of the disease and the side effects of pharmacotherapy, as well as to learn the exact mechanisms of their occurrence. Modern research allows us to understand the possible causes of these disorders, but there is still much to discover. Therefore, research on the intestinal microbiota can provide a lot of interesting information that facilitates the treatment of mental illnesses.

***Table 1***. Overview of studies reporting the effects of various bacteria strains on mental health (own elaboration)

| Strain of bacteria | The disease it affects | Literature |
|---|---|---|
| *Lactobacillus spp., Bifidobacterium spp., Escherichia spp., Enterococcus spp., Bacillus spp., Saccharomyces spp.,* | Depression | [2], [7], [10], [16] |
| *Bifidobacterium spp., Lactobacillus spp., Sutterella spp., Prevotella spp., Ruminococcus spp.,* | Autism | [17] |
| *Haemophilus spp., Sutterella spp., Clostridium spp., Ruminococcus spp., Anaerococcus spp.,* | Schizophrenia | [21], [22] |
| *Firmicutes spp., Faecalibacterium spp., Lactobacillus spp., Bifidobacterium spp.,* | Bipolar Disorder | [20] |
| *Bifidobacterium spp., Firmicutes spp., Ruminococcus spp., Enterococcus spp.,* | ADHD | [2], [26], [27] |


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