SIEJKA, Agata, WANAT, Joanna, HOMA, Wojciech, DZIKOWSKA, Izabela, STEFANIAK, Daria, ZIELIŃSKA, Weronika, CHRÓL, Michal, WARUNEK, Aleksandra and GRONOWICZ, Gabriela. The Brain-Gut-Microbiota Axis in Depression: Medical Progress. Journal of Education, Health and Sport. 2025;79:58446. eISSN 2391-8306.
https://doi.org/10.12775/JEHS.2025.79.58446
https://apcz.umk.pl/JEHS/article/view/58446

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 02.02.2025. Revised: 02.03.2025. Accepted: 02.03.2025. Published: 03.03.2025.

The Brain-Gut-Microbiota Axis in Depression: Medical Progress

1. Agata Siejka

Medical University of Lublin

Aleje Racławickie 1, 20-059 Lublin

agata.siejka12@gmail.com

ORCID: 0009-0009-2332-0115

2. Joanna Wanat

Medical University of Lublin

Aleje Racławickie 1, 20-059 Lublin

asiawanat2000@gmail.com

ORCID: 0009-0009-3349-3618

3. Wojciech Homa

Wojewódzki Szpital Specjalistyczny

al. Kraśnicka 100, 20-718 Lublin

wojciech.homa2@gmail.com

ORCID: 0000-0003-2177-8818

4. Izabela Dzikowska
Medical University of Lublin
Aleje Racławickie 1, 20-059 Lublin
dzikowskaizabela2@gmail.com
ORCID: 0009-0006-5539-3771

5. Daria Stefaniak
Medical University of Lublin
Aleje Racławickie 1, 20-059 Lublin
dariastefaniak18@gmail.com
ORCID: 0009-0002-2207-4177

6. Weronika Zielińska
Medical University of Lublin
Aleje Racławickie 1, 20-059 Lublin
w09290929@gmail.com
ORCID: 0009-0007-0707-9590

7. Michał Chról
Medical University of Lublin
Aleje Racławickie 1, 20-059 Lublin
michuGBE@gmail.com
ORCID: 0009-0005-7776-6260

8. Aleksandra Warunek
Medical University of Lublin
Aleje Racławickie 1, 20-059 Lublin
warunek.aleks@gmail.com
ORCID: 0009-0000-7542-6522

9. Gabriela Gronowicz
Medical University of Lublin
Aleje Racławickie 1, 20-059 Lublin
gabagronowicz@gmail.com

ORCID: 0009-0009-4034-1284

ABSTRACT:

Introduction and Purpose: In recent years, more and more scientific research has paid attention to determining the role of gut microbiota in maintaining the body's homeostasis. It is attributed not only to the functions related to digestion but also to many others that may seem unrelated to the digestive tract. This includes, among others, creating immunity and psyche, through a strong influence on the gut-brain axis. The gut microbiota colonizes the digestive tract already in the first days after birth. Over time it undergoes significant changes, both quantitative and qualitative. This affects the ability to perform the functions mentioned above. This study aims to review current scientific research on the gut microbiota and the gut-brain axis and to determine how they may participate in the pathogenesis of depressive disorders.

Brief Description of the State of Knowledge: Changes in the number and proportion of microorganisms that create the gut microbiota are associated with severe disorders. Disturbances in the gut-brain axis can affect many processes, which are the basis of neurological and psychiatric conditions. Due to the prevalence and limitations of currently used methods of treating depressive disorders, scientists emphasize the necessity of perceiving this disease as one of the symptoms of a disturbed gut-brain axis. Understanding the entire pathophysiology could help in defining strict procedures for the treatment of the aforementioned dysbiosis.

Summary: Depression affects a significant group of patients in everyday medical practice. Even for experienced doctors, it is a major diagnostic and therapeutic challenge. Diagnosis, treatment, and prevention of gut dysbiosis may prove to be an effective support for classic depression therapy.

Materials and Methods: The literature review was conducted using the PubMed database.

Key words: gut microbiota, dysbiosis, gut- brain axis, depression, major depressive disorder, probiotic

INTRODUCTION:

The Gut Microbiota

At the beginning of our consideration, we have to explain what microbiota is and what important functions it has in our body. The gut microbiota can be defined as the trillions of microorganisms that inhabit the digestive systems of all animals, including humans [1, 2]. The population of microorganisms is about ten times bigger than the number of cells in our body [3]. It is assumed that they can weigh up to 2 kg [4]. The gut microbiota consists of bacteria, viruses, fungi, protists, archaea, their genomes and the environment around them. The vast majority, as much as 90%, are bacteria, mainly from two genera: *Bacteroidetes* and *Firmicutes* [5].

It is common knowledge that gut microbiota plays a key role in maintaining proper digestive function and regulating pH, peristalsis, and bowel movement rhythm. It aids digestion, nutrient absorption, fat metabolism, and vitamin synthesis, particularly B vitamins. The anaerobic fermentation of fiber produces short-chain fatty acids (SCFAs) that provide energy to colon cells, with butyric acid crucial for their growth and differentiation. The microbiota also helps neutralize toxins and carcinogens [6, 7, 8]. However, the role of the gut microbiota is not limited only to processes related to food digestion and its passage. Unfortunately, a lot of people still don't realize that gut microbiota fulfills other equally important functions such as participation in the synthesis of serotonin, also known as the happiness hormone, modulation of the hypothalamic-pituitary-adrenal (HPA) axis, and conduction in the vagus nerve, which is most of the parasympathetic fibers in our body. Additionally, it takes part in regulating the immune system. It has immunomodulatory effects, influences cytokine levels, and interacts with the digestive tract's lymphatic tissue, which is the largest lymphatic organ in the human body [8]. Given these facts, there is no doubt that any imbalances in the quantity and composition of the gut microbiota can lead to serious metabolism and systemic problems, relating to disorders in peristalsis, digestion, absorption, and vitamin production, as well as

the breakdown of the intestinal barrier, excessive immune system activation and dysregulation of neurology and endocrine system [9, 10].

The gut microbiome is formed throughout life and many factors influence its composition and functions. Its creation begins as a baby passes through the mother's birth canal during delivery. After birth, the diet has a primary role in building and modulating the microbiota as it adapts to absorbed nutrients. Feeding methods in infancy have a significant impact on the microbiome's arrangement, and the first year of life is a crucial period for development. At birth, taxonomic diversity is low but increases over time [11, 12, 13]. Factors that negatively affect the gut microbiome include cesarean delivery, short or no breastfeeding, introduction of solid foods before 3 months of age, antibiotic use during pregnancy or early life, and poor dietary habits, especially high consumption of ultra-processed foods [14]. Exercise promotes microbiota diversity by supporting a healthy lifestyle, reducing inflammation, lowering disease risk, and improving metabolic markers [15]. On the other hand, antibiotics disrupt the microbiota by killing both harmful and beneficial microbes, leading to dysbiosis. The type and duration of antibiotic treatment influence the extent of this disruption [16]. Smoking, including e-cigarettes, also affects microbiota composition, particularly in the oral cavity. In general, factors such as nutrition based on unbalanced and highly processed meals, lifestyle with a predominance of sedentarism, drug use, smoking, alcohol consumption, hormonal changes, decreased immunity, high antibiotic use, health situation, and possibly disorder of the gut-brain axis (related to stress, depression, autism) negatively impact the gut microbiome’s composition and function [2, 17].

The Gut-Brain Axis

Many studies and scientific papers created in the last decades have focused on the presence of a functional relationship between the digestive tract, gut microbiota, and the brain. The issue of disturbances in the correlation mentioned above may concern many patients from various areas of medicine, suffering from diseases in the treatment of which pharmacotherapy has not brought the desired effects or has caused the occurrence of numerous serious adverse effects. The discovery of another possible method of therapy has given hope to patients and their doctors for curing and improving the quality of life. This is why the issue of the gut-brain axis

is such a dynamically developing area of medicine, in which we place great expectations [18,19].

The specific relationship between the gastrointestinal tract and the central nervous system (CNS) has been called the "gut-brain axis" and involves the bidirectional (afferent and efferent) exchange of neural, endocrine, and immune signals between them [20]. This is an integrated physiological concept. This axis is considered bidirectional, which means that the intestines can regulate the functioning and emotional activity in the CNS, and the CNS can regulate the functioning of the gastrointestinal tract [21]. However, previous studies have not shown the chronological order of disorders, so it is not known exactly whether disorders in the functioning and emotional activity of the CNS cause gut dysbiosis, or whether changes in the amount or composition of the gut microbiota promote disorders of the CNS [2].

The bidirectional communication between the gut, its microbiota, and the CNS is organized at four distinct levels: metabolic, nervous, neuroendocrine, and immunological. Transmission at the level of neurotransmitters, neuropeptides, microbiome-derived products (mainly bacterial metabolites), and maintenance of the integrity of the intestinal barrier and tight junctions also play an important role [22, 23].

Communication at the neural level involves the modulation of signals conducted by the vagus nerve. Regulation of the gut-brain axis at the neuroendocrine level occurs primarily through the HPA axis, also known as the stress axis, which primarily controls the stress response through the synthesis of cortisol. The thesis based on gut-brain communication at the immunological level indicates the production of immune mediators (mainly cytokines) in reaction to persistent inflammation as a result of increased intestinal permeability (also known as leaky gut syndrome (LGS)). The importance of communication at the level of using neurotransmitters and neuropeptides is the fact that the gut microbiota can influence the synthesis or metabolism of neurotransmitters or produce these neuroactive substances themselves. In addition, the gut microbiota has enzymes that control the pathways of tryptophan metabolism leading to the formation of serotonin. Microbiome-derived products (which are mainly bacterial metabolic products) such as SCFAs play a particular role in gut integrity [2, 19, 23, 24].

The fundamental communication tracks between the gut microbiota and the brain appear to be the vagus nerve, tryptophan metabolites, and microbial products- SCFAs [19].

The Neuronal Pathways

The neuroanatomical level of the gut-brain axis involves two pathways: a direct connection between the brain and intestines via the vagus nerve and the autonomic nervous system (ANS), and an indirect route connecting the enteric nervous system (ENS) to the ANS [22]. The researchers have shown that 90% of impulses in the brain-gut axis are transmitted centripetal, i.e. from the gut to the brain, and only 10% centrally from the brain to the gut [25]. These pathways play a significant role in gut-brain axis disturbances generally manifesting as various mental disorders. The gut microbiota supports anti-stress and anti-anxiety responses by modulating vagus nerve activity and secreting neurotransmitters including γ-aminobutyric acid (GABA) (produced by *Lactobacillus* and *Bifidobacterium*), acetylcholine (*Lactobacillus*), serotonin (*Escherichia*, *Candida*, *Enterococcus*), dopamine (*Bacillus*), and noradrenaline (*Bacillus*, *Saccharomyces*) and SCFAs [25, 26]. Chronic vagus nerve stimulation (VNS) reduces anxiety through alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR)- mediated excitatory neurotransmission [27], while transcutaneous auricular VNS has shown effectiveness in treating depression, comparable to traditional depression pharmacotherapy [28]. Elevated vagal tone also reduces cytokine production, demonstrating immunomodulatory effects [29]. The role of substances produced by gut microbiota is not limited to participating in communication within the intestinal flora. These substances play a role in systemic and peripheral processes that influence brain function. The gut microbiota also regulates the levels and metabolism of glutamic acid (glutamate), a key neurotransmitter in the CNS involved in learning and memory. While essential under normal conditions, excessive glutamate can overstimulate receptors and harm neurons. Glutamate is also converted into GABA, the main inhibitory neurotransmitter, and the microbiota affects both GABA levels and its metabolism [23, 30].

The Endocrine Pathways

At the neuroendocrine level, a fundamental role plays the HPA axis. This axis is one of the main mechanisms regulating the course of the stress response. HPA axis begins in the paraventricular nucleus of the hypothalamus, where takes place the synthesis of two hypothalamic hormones: corticotropin-releasing hormone (CRH) and vasopressin. These

hormones start a hormonal cascade along the HPA axis. The function of CRH is to stimulate the anterior pituitary gland to produce and secrete the adrenocorticotropic hormone (ACTH). ACTH goes through the blood to the adrenal cortex and stimulates it to secrete glucocorticoids, mainly cortisol [22]. On the other hand, the gut microbiota modulates the availability of nutrients and influences the secretion of biologically active peptides from enteroendocrine cells. This change in peptide release may impact the functioning of the gut-brain axis. For this reason, the neuropeptide galanin increases the activity of the central component of the HPA axis, resulting in modified secretion of corticotropin-releasing factors (CRF) and ACTH. This stimulation leads to increased secretion of glucocorticoids from the adrenal cortex [24, 31]. Cortisol exerts its effects on the CNS through hormonal and neural communication pathways. These interacting pathways influence the activity of various cell types in the gut, including intestinal effector cells, smooth muscle cells, epithelial cells, enterochromaffin cells, interstitial cells of Cajal, enteric neurons, and immune cells [32]. In addition, cortisol plays a crucial role in the endocrine mechanisms regulating the gut-brain axis, as it affects immune cells by modulating the secretion of cytokines acting on the HPA axis. Consequently, stress conditions lead to changes in the gut microbiome, immune function, mucus production, gut motility, and permeability [33].

The Immune Pathways

In recent years, increasing evidence suggests that disorders of the gut-brain axis may have an inflammatory basis, which patients most often manifest as various psychiatric illnesses. Inflammatory mediators induce changes in brain functions at the neurohormonal and neurochemical levels, which may be displayed in numerous diseases from the neurological and psychiatric areas [34]. Increased intestinal permeability, LGS, is a fundamental factor in initiating a systemic inflammatory response. LGS is associated with disruption of the gut microbiota, enterocyte damage, and weakening of tight junctions between enterocytes [35, 36]. This process causes the translocation of Gram-negative bacteria containing lipopolysaccharide (LPS) in the cell membrane structure, which triggers a cascade of reactions leading to the activation of the immune system [37]. As a result of the described changes, immune cells produce pro-inflammatory cytokines (IL-6, IFN-γ, CRP, TNF-α), which initiates the development of a generalized inflammation of the body and hurts cells, including cells of the CNS [38]. Another consequence of increased levels of pro-inflammatory cytokines is an

activation of the limbic system, which is responsible for memory, emotions, and behavior. Through the HPA axis, stress generated as a defense mechanism in reaction to systemic inflammation causes the secretion of cortisol from the adrenal cortex, which triggers many responses, including changes in brain function. Modifications in the gut microbiota, such as a decrease in the number of beneficial *Lactobacillus* and *Bifidobacteria* bacteria, also impact the body's answer to external factors [19].

In summary, disorders in the structure and function of the gut microbiota lead to increased permeability and penetration of substances that affect physiological processes, which activate the immune response and cause chronic inflammation. Chronic inflammation, which is most often accompanied by disturbances of the gut microbiota, may be a factor initiating the development of a wide range of neuropsychiatric diseases. Based on this information, it seems certain that neuropsychiatric disorders and inflammation are closely related [19, 23, 34].

Neurotransmitters and Neuropeptides

One of the important examples that should be also mentioned is the influence of the gut microbiota on the brain-gut axis through the production of neuroactive substances, known as neurotransmitters. It is mainly based on the synthesis of serotonin, often called the happiness hormone. Deficiency of this neurotransmitter in the CNS is considered a critical factor leading to depression, sadness, apathy, and anxiety. Nowadays theories indicate it as the main cause of the development of a depressive episode [39]. The gut microbiota contains enzymes that control the processes of metabolism of the serotonin precursor, which is tryptophan. This is an amino acid necessary for the proper functioning of our body, of which about 2% supplied with food is converted into serotonin. In the human organism, serotonin is mainly produced in the digestive tract, nervous system, and immune system. As much as 95% of the total score of serotonin is produced in the gastrointestinal tract by enterochromaffin cells (ECC) of the mucosa, intestinal microorganisms, and neurons located in the neural plexuses of the submucosal and muscular layers. The remaining 3% of serotonin is produced in platelets and 2% in the pineal gland. In the nervous system, serotonin is a neurotransmitter that plays a primary role in regulating pain, sleep, mood, and memory processes [40, 41, 42]. Due to the blood-brain barrier (BBB), all neurotransmitters synthesized in the intestines do not reach the brain directly, except GABA, which is transported across the BBB thanks to specific transporters [19]. An additional pathway for the influence of intestinal neurotransmitters on

the brain is indirect communication through the enteric nervous system (ENS). Serotonin is the most important transmitter in the nervous system of the gastrointestinal tract, where its receptors are located in the neurons of the submucosal and muscular plexuses, enterocytes, and smooth muscle cells. Through specific receptors, serotonin affects the activity of the gastrointestinal tract, both inhibiting and stimulating its functions [41]. Studies have shown that serotonin metabolism disorders are responsible for the pathogenesis of some gastrointestinal diseases. For example, increased serum serotonin levels have been observed in inflammatory bowel diseases (IBD), intestinal infections, or appendicitis [43]. Moreover, it has been found that intestinal bacteria, such as *Bifidobacterium infantis*, can influence the level and metabolism of tryptophan, increasing its availability in the body [44]. In this way, the gut microbiota, by controlling the amount of tryptophan - the precursor of serotonin - also affects the level of serotonin in the brain [23, 24].

Bacterial Metabolites

The bacterial products of metabolism have a special role in regulating the brain-gut axis. The proven importance is mainly SCFAs. They are produced by bacterial fermentation of dietary fiber in anaerobic conditions. 95% of the SCFAs produced in the intestines are 3 acids: butyric acid (butyrate), acetic acid (acetate), and propionic acid (propionate), and in smaller amounts lactic acid [23, 45]. The main producers are bacteria of the genus *Clostridium spp., Eubacterium spp., Fusobacterium spp., Butyrivibrio spp., Megasphaera elsdenii, Mitsuokella multiacida, Rosburia intestinalis, Faecalibacterium prausnitzii, and Eubacterium hallii* [46]. Butyrate is a primary source of energy for colonocytes while stimulating their growth and differentiation. SCFAs have many functions in the human body. They support the development of beneficial intestinal microorganisms while inhibiting the development of pathogenic bacteria such as *E. coli, Campylobacter sp., or Salmonella sp.,* which compete with healthful microflora for space to colonize [25, 47]. In addition, SCFAs support the regeneration and proper functioning of the intestinal epithelium, stimulate mucus production, maintain appropriate intestinal pH, and protect the gastrointestinal tract from microbiota disorders. Moreover, they strengthen the intestinal barrier by limiting the absorption of inulin, which promotes the development of beneficial microflora. SCFAs also have anti-inflammatory effects, including inhibiting inflammatory mediators, reducing IL-8 secretion, and blocking the proinflammatory cytokine cascade [25]. The deficiency of bacteria-

producing SCFAs can lead to brain disorders. Studies on mice deprived of bacterial microbiota have shown serious problems in the development of microglial cells [48] and changes in the neurotransmitter and receptor systems in various areas of the brain [49]. The most important factor seems to be the observed increase in serotonin levels in the hippocampus with a simultaneous reduction in the expression of its receptors. In mice with gut dysbiosis, significant abnormalities in the functioning of some cells were improved after the restoration of a diverse microbiota [50]. What is more important, SCFAs supplementation also improved the functioning of microglial cells [49].

Depression

Major Depressive Disorder (MDD) is a mental disease that is one of the most common causes of disability, morbidity, and mortality in developed countries. Due to its prevalence and the consequences it has, MDD remains a serious challenge for today's medicine [51].
More than 264 million people suffer from this disease worldwide, of whom about 800 thousand commit suicide each year. However, it is calculated that the number of people suffering from depressive disorders, both clinical and subclinical, may be much bigger, but these people remain undiagnosed [52, 53].

The main symptoms of MDD include low mood, reduced energy or increased fatigue, loss of interest or anhedonia, unjustified feelings of guilt, disturbances in cognitive processes such as concentration and memory, thoughts of resignation or suicidal thoughts and tendencies, anxiety, somatic complaints, lowered appetite, weight loss, and sleep problems. To be able to make a diagnosis of MDD, these signs must persist for at least 14 days [54].

The consequences of depression are very diverse and include a deterioration in the quality of life, health problems, impaired social functioning, increased unemployment, reduced productivity, and a raised need for support from the healthcare system [55].

The exact mechanisms of the development of MDD are still unproven, but scientists suggest that a hypothesis based on deficiency in monoamine neurotransmitters such as serotonin, norepinephrine, and dopamine is the most probable one [56]. An equally important factor is

chronic inflammation in the organism, which leads to raised levels of proinflammatory cytokines and activation of microglia and astrocytes in the brain. Such changes can influence the functioning of the nervous system, behaviors, and emotions, which contributes to the development of MDD [57].

As mentioned above, gut-brain communication is bidirectional. In this communication, the gut microbiota plays a key role. Clinical studies have shown significant changes in the gut microbiota composition in patients with MDD compared to healthy people. They mainly consisted of an increased number of *Bacteroidetes* and *Proteobacteria* bacteria and a reduced number of *Firmicutes*, *Bifidobacterium*, and *Lactobacillus*. [58, 59, 60]. Moreover, the presence of bacteria producing SCFAs, such as *Coprococcus*, is associated with a better quality of life manifested by physical and emotional well-being, vitality, and good social functioning. In people with depression, there is a decrease in the number of *Coprococcus* bacteria [61]. Studies have also shown that the use of probiotics can improve mental health by restoring the proper composition of the gut microbiota, which also confirms the significant associations between depression and the gut microbiota [62].

Direct or indirect production of neurotransmitters by gut microbiota significantly affects receptors in the central nervous system or peripheral receptors belonging to neuronal or immune cells. This statement can be confirmed by the study in which chronic supplementation of *L. rhamnosus* to mice converted the expression of GABA A and GABA B receptors along with changes in brain activity levels, resulting in reduced symptoms of anxiety and depression [63]. Increased production of serotonin (5-HT) in the gut does not lead to raised central 5-HT concentrations because of the BBB. Central 5-HT levels may be increased by intensified production in the gastrointestinal tract of its precursor, known as tryptophan [64, 65].

SCFAs are produced in the colon by anaerobic fermentation of indigestible carbohydrates. Their functions include cross-feeding other bacteria and, after absorption in the large intestine, modulating the function of the immune, digestive, and nervous systems. Studies in mice have shown that the supplementation of the three most important SCFAs- acetate, butyrate, and propionate- can relieve symptoms of depression [66]. Another study confirmed that a group of patients with MDD had lower levels of some gut microbiomes, including butyrate-producing bacteria [67]. This suggests that changes in these gut bacteria may be involved in the pathogenesis of MDD .

The gut microbiota has an important role in psychiatric disorders at the intestinal level, which is associated with the weakening of the intestinal barrier, typical of intestinal dysbiosis. This is about the LGS already discussed. The weakening of this barrier is associated with the displacement of various substances outside the intestinal tract and the induction of a generalized inflammatory reaction. Increased production of proinflammatory cytokines in patients with symptoms of depression is a common result in clinical studies. These cytokines include IL-1β, IL-6, TNF-α, interferon-gamma, and increased concentration of C-reactive protein. It is known that the gut microbiota regulates the transcription of these cytokines, and dysbiosis activates the inflammatory reaction [68]. On the other hand, beneficial metabolites, such as SCFAs, limit the production of proinflammatory cytokines, including IL-1 [69].
Another important component of the pathogenesis of depression is the HPA axis, which modulates the stress response. The hypothalamus, as a result of the secretion of CRH, stimulates the pituitary gland to synthesize and release ACTH into the blood vessels. ACTH causes the release of cortisol from the adrenal cortex. Excessive activity of this axis leads to a proportionate increase in cortisol levels, which can affect the changes in intestinal integrity, motor function, mucus production, and the composition of the gut microbiota, intensifying the symptoms of depression [70].

Standard therapy for MDD includes antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCA), and monoamine oxidase inhibitors (MAOIs). They affect on availability of neurotransmitters in the synaptic cleft. However, these therapies have some restrictions, including delayed onset of activity, increased tolerance, side effects, the necessity to stop the treatment after 2 years, and limited effectiveness after longer periods of use [71]. Therefore, new therapeutic strategies are desired, and the modification of the gut microbiota is one of the very promising directions. Studies indicate that fecal microbiota transplantation (FMT) and probiotic supplementation can have a beneficial effect on mental health and alleviate symptoms of depression. Thanks to more advanced technologies, research on the gut microbiota as a potential therapeutic purpose is gaining momentum and provides new hope for patients with MDD [17, 18].

Treatments of Depression

Traditional Treatment

Traditional methods of curing depression include psychotherapy, pharmacotherapy, and electroconvulsive therapy, and the selection of the appropriate form of therapy depends on the stage of the disease. Psychotherapy and pharmacotherapy are the most often chosen in patients with mild or moderate symptoms. In turn, electroconvulsive therapy is reserved for severe degrees of depression, especially life-threatening or resistant to other forms of treatment. Pharmacotherapy is mainly based on the use of SSRIs [18]. It is worth emphasizing that the latest studies show that traditional depression medicines affect not only the nervous system but also the intestinal microbiota. For example, serotonin, in addition to its antidepressant effect, also helps improve the structure of the intestinal microbiome [72]. However, the traditional cure for depression has limitations, such as delayed activity, drug tolerance, insufficiently satisfactory effects, and side effects. For this reason, the search for new forms of therapy, including the use of intestinal microbiota, is currently the subject of many studies [73].

Diet

Diet has a fundamental role in creating and modulating the gut microbiome. Clinical studies show that dietary changes within 24 hours can have a positive impact on the gut microbiota [74]. Therefore, improving the diet and introducing healthy eating habits can be valuable support in the treatment of depression. Combining a healthy lifestyle with the Mediterranean diet (MD) or ketogenic diet (KD) can protect against the development of depression [73, 75]. On the other hand, a Western diet rich in calories, saturated fats, and sugars leads to gut dysbiosis, promoting the proliferation of pro-inflammatory bacteria and limited functioning of beneficial ones, producing SCFAs. This causes inflammation, oxidative stress, and impaired neurogenesis. In turn, Mediterranean, ketogenic, as well as vegetarian or vegan diets are associated with a lower risk of depression by promoting microbiota balance, reducing inflammation, and increasing brain-derived neurotrophic factor (BDNF) and GABA levels [73, 76, 77].

Prebiotics, probiotics, and postbiotics

Prebiotics, probiotics, and postbiotics are other promising courses of research in depression therapy.

- Prebiotics are non-digestible food ingredients, mainly polysaccharides, that support the growth and activity of beneficial microorganisms that colonize the human digestive tract. Through bacterial fermentation, prebiotics contribute to the production of SCFAs, such as butyric acid, acetic acid, or propionic acid. They support intestinal well-being, high level of immunity, and increased mineral absorption. Prebiotics can be a source of energy for the gut microbiome, and work antagonistically against pathogenic bacteria [8,78,79].

- Probiotics are alive microorganisms that have a beneficial effect on the organism when supplemented in appropriate amounts. Probiotics support the structure of the gut microbiota and improve the function of the intestinal barrier by developing a healthy mucosal layer and inhibiting endotoxemia [80, 81]. In addition, they reduce inflammation by inhibiting the induction of the cytokine IL-8 in the human colon epithelium [82]. The most commonly used strains are *Lactobacillus*, *Bifidobacterium*, and selected strains of *Streptococcus* and *Enterococcus*. Most bacteria are acquired at birth and then adapted depending on the diet. In healthy people who follow a balanced diet, there is a proportion in the composition of the intestinal microbiota. Otherwise, there are indications to consider additional supplementation of probiotic bacteria [83].

- Postbiotics are inactivated microorganisms and their metabolites that support health similar to probiotics by maintaining the function of the epithelial barrier, modulating immunity, and influencing metabolism [8, 84].

Clinical studies have shown that probiotics have more significant potential than prebiotics or postbiotics in relieving symptoms of depression [8]. In one research, patients with intermediate-stage depression were given a symbiotic in combination with fluoxetine, which resulted in notable reductions in symptoms compared to the placebo group [85].

Although there is a need for additional research, it is already evident that probiotics and dietary interventions, mainly the MD, can complete standard antidepressant treatment and

reduce the side effects of the drugs [73]. To prevent neurological disorders it is crucial to avoid dysbiosis, especially during pregnancy and early childhood [17].

Summary: The reviewed research papers and articles confirm that disorders in microbiota composition contribute to the development of mental and psychiatric diseases. Understanding the bidirectional gut-brain axis delivers valuable insights for creating new therapies. Diet influences the gut microbiota and the production of its metabolites in the gut. Research on probiotic supplementation highlights the connection between microbiota and mood disorders, as well as probiotics' potential in alleviating symptoms. This paves the way for alternative treatments for mood disorders.

Conclusions: This review analyzed the two-way communication between the gut and brain through the gut-brain axis, focusing on the role of gut microbiota in the development of depression. To better understand these connections, further research needs to investigate gut bacteria in larger populations with mental disorders, including the impact of medications and diet. Expanding this knowledge is crucial for developing prevention strategies and new treatments for mental health conditions. Next studies should focus also on determining the optimal doses, timing, and combinations of probiotics with current standard pharmacotherapy (antidepressants) to maximize the effectiveness of therapy.

Disclosures

Author's contribution:

Conceptualization: Agata Siejka
Methodology: Joanna Wanat, Izabela Dzikowska, Daria Stefaniak
Formal analysis: Wojciech Homa, Weronika Zielińska, Michał Chról
Investigation: Gabriela Gronowicz, Aleksandra Warunek, Izabela Dzikowska
Data curation: Agata Siejka, Joanna Wanat, Wojciech Homa
Writing - rough preparation: Agata Siejka, Daria Stefaniak, Aleksandra Warunek, Gabriela Gronowicz
Writing - review and editing: Michał Chról, Weronika Zielińska
Supervision: Agata Siejka, Joanna Wanat

Project administration: Agata Siejka, Wojciech Homa
All authors have read and agreed with the published version of the manuscript.

Founding Statement: The study did not receive funding.
Institutional Review Board Statement: Not applicable.
Informed Consent Statement: Not applicable.
Data Availability Statement: Not applicable.
Conflict of Interest Statement: The authors declare no conflicts of interest.
Acknowledgments: Not applicable.

References:

1. Gomaa E.Z. Human gut microbiota/microbiome in health and diseases: A review. Antonie Van Leeuwenhoek Int. J. Gen. Mol. Microbiol. 2020;113:2019–2040. doi: 10.1007/s10482-020-01474-7 PMID: 33136284.

2. Młynarska E., Gadzinowska J., Tokarek J, Forycka J., Szuman A., Franczyk, B. Rysz J. The Role of the Microbiome-Brain-Gut Axis in the Pathogenesis of Depressive Disorder Nutrients. 2022 May 4;14(9):1921. doi: 10.3390/nu14091921 PMCID: PMC9105444 PMID: 35565888.

3. Adak A., Khan M.R. An insight into gut microbiota and its functionalities. Cell. Mol. Life Sci. 2019;76:473–493. doi: 10.1007/s00018-018-2943-4 PMID: 30317530 PMCID: PMC11105460.

4. Flint H.J. The impact of nutrition on the human microbiome. Nutr. Rev. 2012;70:S10–S13. doi: 10.1111/j.1753-4887.2012.00499.x, PMID: 22861801.

5. Jandhyala S.M., Talukdar R., Subramanyam C., Vuyyuru H., Sasikala M., Reddy D.N. Role of the normal gut microbiota. World J. Gastroenterol. 2015;21:8787. doi: 10.3748/wjg.v21.i29.8787, PMID: 26269668 PMCID: PMC4528021.

6. Yadav M., Verma M.K., Chauhan N.S. A review of metabolic potential of human gut microbiome in human nutrition. Arch. Microbiol. 2018;200:203–217. doi: 10.1007/s00203-017-1459-x, PMID: 29188341.

7. Turnbaugh P.J., Ley R.E., Hamady M., Fraser-Liggett C.M., Knight R., Gordon J.I. The human microbiome project. Nature. 2007;449:804–810. doi: 10.1038/nature06244, PMID: 17943116 PMCID: PMC3709439.

8. Chudzik A., Orzyłowska A., Rola R., Stanisz G. J., Probiotics, Prebiotics and Postbiotics on Mitigation of Depression Symptoms: Modulation of the Brain–Gut–Microbiome Axis, Biomolecules. 2021 Jul 7;11(7):1000. doi: 10.3390/biom11071000, PMCID: PMC8301955 PMID: 34356624.

9. Yang Z., Li J., Gui X., Shi X., Bao Z., Han H., Li M.D. Updated review of research on the gut microbiota and their relation to depression in animals and human beings. Mol. Psychiatry. 2020;25:2759–2772. doi: 10.1038/s41380-020-0729-1, PMID: 32332994.

10. Bravo J.A., Julio-Pieper M., Forsythe P., Kunze W., Dinan T.G., Bienenstock J., Cryan J.F. Communication between Gastrointestinal Bacteria and the Nervous System. Curr. Opin. Pharmacol. 2012;12:667–672. doi: 10.1016/j.coph.2012.09.010, PMID: 23041079.

11. Thompson A.L., Monteagudo-Mera A., Cadenas M.B., Lampl M.L., Azcarate-Peril M.A. Milk- and solid-feeding practices and daycare attendance are associated with differences in bacterial diversity, predominant communities, and metabolic and immune function of the infant gut microbiome. Front. Cell. Infect. Microbiol. 2015;5:3. doi: 10.3389/fcimb.2015.00003, PMID: 25705611 PMCID: PMC4318912.

12. Lee S.A., Lim J.Y., Kim B.S., Cho S.J., Kim N.Y., Kim O.B., Kim Y. Comparison of the gut microbiota profile in breast-fed and formula-fed Korean infants using pyrosequencing. Nutr. Res. Pract. 2015;9:242–248. doi: 10.4162/nrp.2015.9.3.242, PMID: 26060535 PMCID: PMC4460055.

13. Mariat D., Firmesse O., Levenez F., Guimaraes V.D., Sokol H., Dore J., Corthier G., Furet J.P. The Firmicutes/Bacteroidetes ratio of the human microbiota changes with age. BMC Microbiol. 2009;9:123. doi: 10.1186/1471-2180-9-123, PMID: 19508720 PMCID: PMC2702274.

14. Parkin K, Christophersen C T, Verhasselt V, Cooper M N, Martino D. Risk Factors for Gut Dysbiosis in Early Life. Microorganisms. 2021;9(10):9. doi: 10.3390/microorganisms9102066 PMID: 34683389 PMCID: PMC8541535.

15. Limbana T., Khan F., Eskander N. Gut Microbiome and Depression: How Microbes Affect the Way We Think. Cureus. 2020;12:e9966. doi: 10.7759/cureus.9966, PMID: 32983670 PMCID: PMC7510518.

16. Klingensmith N.J., Coopersmith C.M. The Gut as the Motor of Multiple Organ Dysfunction in Critical Illness. Crit. Care Clin. 2016;32:203–212. doi: 10.1016/j.ccc.2015.11.004, PMID: 27016162 PMCID: PMC4808565.

17. Naufel M.F., Truzzi G.M., Ferreira M. C., Santos Coehlo F.M., The brain-gut-microbiota axis in the treatment of neurologic and psychiatric disorders, Arq Neuropsiquiatr. 2023 Jul 4;81(7):670–684. doi: 10.1055/s-0043-1767818, PMCID: PMC10371417 PMID: 37402401.

18. Zhu F., Tu H., Chen T., The Microbiota–Gut–Brain Axis in Depression: The Potential Pathophysiological Mechanisms and Microbiota Combined Antidepression Effect, Nutrients. 2022 May 16;14(10):2081. doi: 10.3390/nu14102081, PMCID: PMC9144102 PMID: 35631224.

19. Socała K., Doboszewska U., Szopa A., Serefko A., Włodarczyk M., Zielińska A., Poleszak E., Fichna J., Wlaź P., The role of microbiota-gut-brain axis in neuropsychiatric and neurological disorders, Pharmacol Res. 2021 Oct;172:105840. doi: 10.1016/j.phrs.2021.105840. Epub 2021 Aug 24. PMID: 34450312.

20. Morais L.H., Schreiber H.L.t., Mazmanian S.K. The gut microbiota-brain axis in behaviour and brain disorders. Nat. Rev. Microbiol. 2021;19:241–255. doi: 10.1038/s41579-020-00460-0 PMID: 33093662.

21. Osadchiy V., Martin C.R., Mayer E.A. The Gut-Brain Axis and the Microbiome: Mechanisms and Clinical Implications. Clin. Gastroenterol. Hepatol. 2019;17:322–332. doi: 10.1016/j.cgh.2018.10.002 PMID: 30292888 PMCID: PMC6999848.

22. Spencer R.L., Deak T. A users guide to HPA axis research. Physiol. Behav. 2017;178:43–65. doi: 10.1016/j.physbeh.2016.11.014 PMID: 27871862 PMCID: PMC5451309.

23. Góralczyk- Bińkowska A., Szmajda- Krygier D., Kozłowska E., The Microbiota–Gut–Brain Axis in Psychiatric Disorders, Int J Mol Sci. 2022 Sep 24;23(19):11245. doi: 10.3390/ijms231911245, PMCID: PMC9570195 PMID: 36232548.

24. Toader C, Dobrin N, Costea D, Glavan LA, Covache-Busuioc RA, Dumitrascu DI, Bratu BG, Costin HP, Ciurea AV. Mind, Mood and Microbiota-Gut-Brain Axis in Psychiatric Disorders. Int J Mol Sci. 2024 Mar 15;25(6):3340. doi: 10.3390/ijms25063340. PMID: 38542314; PMCID: PMC10970241.

25. Breit S., Kupferberg A., Rogler G., Hasler G. Vagus nerve as modulator of the brain-gut axis in psychiatric and inflammatory disorders. Front. Psychiatry. 2018;9:44. doi: 10.3389/fpsyt.2018.00044 PMID: 29593576 PMCID: PMC5859128.

26. Dinan T., Borre Y., Cryan J. Genomics of schizophrenia: Time to consider the gut microbiome? Mol. Psychiatry. 2014;19:1252–1257. doi: 10.1038/mp.2014.93 PMID: 25288135.

27. Zhang S.-Q., Xia Z.-X., Deng Q., Yang P.-F., Long L.-H., Wang F., Chen J.-G. Repeated Vagus Nerve Stimulation Produces Anxiolytic Effects via Upregulation of AMPAR Function in Centrolateral Amygdala of Male Rats. Neurobiol. Stress.

2022;18:100453. doi: 10.1016/j.ynstr.2022.100453, PMID: 35685681 PMCID: PMC9170826.

28. Tan C., Qiao M., Ma Y., Luo Y., Fang J., Yang Y. The efficacy and safety of transcutaneous auricular vagus nerve stimulation in the treatment of depressive disorder: A systematic review and meta-analysis of randomized controlled trials. J. Affect. Disord. 2023;337:37–49. doi: 10.1016/j.jad.2023.05.048 PMID: 37230264.

29. Koopman F.A., Chavan S.S., Miljko S., Grazio S., Sokolovic S., Schuurman P.R., Mehta A.D., Levine Y.A., Faltys M., Zitnik R., et al. Vagus Nerve Stimulation Inhibits Cytokine Production and Attenuates Disease Severity in Rheumatoid Arthritis. Proc. Natl. Acad. Sci. USA. 2016;113:8284–8289. doi: 10.1073/pnas.1605635113 PMID: 27382171 PMCID: PMC4961187.

30. Ortega M.A., Alvarez-Mon M.A., García-Montero C., Fraile-Martinez O., Guijarro L.G., Lahera G., Monserrat J., Valls P., Mora F., Rodríguez-Jiménez R., et al. Gut microbiota metabolites in major depressive disorder—Deep insights into their pathophysiological role and potential translational applications. Metabolites. 2022;12:50. doi: 10.3390/metabo12010050 PMID: 35050172 PMCID: PMC8778125.

31. Tortorella C., Neri G., Nussdorfer G.G. Galanin in the regulation of the hypothalamic-pituitary-adrenal axis (Review) Int. J. Mol. Med. 2007;19:639–647. doi: 10.3892/ijmm.19.4.639 .

32. Montagnani M., Bottalico L., Potenza M.A., Charitos I.A., Topi S., Colella M., Santacroce L. The Crosstalk between Gut Microbiota and Nervous System: A Bidirectional Interaction between Microorganisms and Metabolome. Int. J. Mol. Sci. 2023;24:10322. doi: 10.3390/ijms241210322 PMID: 37373470 PMCID: PMC10299104.

33. Wegierska A.E., Charitos I.A., Topi S., Potenza M.A., Montagnani M., Santacroce L. The Connection Between Physical Exercise and Gut Microbiota: Implications for

Competitive Sports Athletes. Sports Med. 2022;52:2355–2369. doi: 10.1007/s40279-022-01696-x PMID: 35596883 PMCID: PMC9474385.

34. Generoso JS, Giridharan VV, Lee J, Macedo D, Barichello T. The role of the microbiota-gut-brain axis in neuropsychiatric disorders. Braz J Psychiatry. 2021 May-Jun;43(3):293-305. doi: 10.1590/1516-4446-2020-0987. PMID: 32667590; PMCID: PMC8136391.

35. Fukui H. Increased intestinal permeability and decreased barrier function: Does it really influence the risk of inflammation? Inflamm. Intest. Dis. 2016;1:135–145. doi: 10.1159/000447252 PMID: 29922669 PMCID: PMC5988153.

36. Camilleri M. Leaky gut: Mechanisms, measurement and clinical implications in humans. Gut. 2019;68:1516–1526. doi: 10.1136/gutjnl-2019-318427 PMID: 31076401 PMCID: PMC6790068.

37. Horn J., Mayer D.E., Chen S., Mayer E.A. Role of diet and its effects on the gut microbiome in the pathophysiology of mental disorders. Transl. Psychiatry. 2022;12:164. doi: 10.1038/s41398-022-01922-0 PMID: 35443740 PMCID: PMC9021202.

38. Allen AP, Dinan TG, Clarke G, Cryan JF. A psychology of the human brain-gut-microbiome axis. Soc Personal Psychol Compass. 2017 Apr;11(4):e12309. doi: 10.1111/spc3.12309. Epub 2017 Apr 18. PMID: 28804508; PMCID: PMC5530613.

39. Donoso F., Cryan J.F., Olavarría-Ramírez L., Nolan Y.M., Clarke G. Inflammation, lifestyle factors, and the microbiome-gut-brain axis: Relevance to depression and antidepressant action. Clin. Pharmacol. Ther. 2022 doi: 10.1002/cpt.2581 PMID: 35278334 PMCID: PMC10084001.

40. Jenkins T.A., Nguyen J.C., Polglaze K.E., Bertrand P.P. Influence of tryptophan and serotonin on mood and cognition with a possible role of the gut-brain axis. Nutrients. 2016;8:56. doi: 10.3390/nu8010056 PMID: 26805875 PMCID: PMC4728667.

41. Terry N., Margolis K.G. Serotonergic Mechanisms Regulating the GI Tract: Experimental Evidence and Therapeutic Relevance. Handb. Exp. Pharmacol. 2017;239:319–342. doi: 10.1007/164_2016_103 PMID: 28035530 PMCID: PMC5526216.

42. Lv J., Liu F. The role of serotonin beyond the central nervous system during embryogenesis. Front. Cell. Neurosci. 2017;11:74. doi: 10.3389/fnpit.2017.00400 PMID: 28348520 PMCID: PMC5346549.

43. Ghia J.E., Li N., Wang H., Collins M., Deng Y., El-Sharkawy R.T., Côté F., Mallet J., Khan W.I. Serotonin has a key role in pathogenesis of experimental colitis. Gastroenterology. 2009;137:1649–1660. doi: 10.1053/j.gastro.2009.08.041PMID: 19706294.

44. Cryan J., Dinan T. Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. Nat. Rev. Neurosci. 2012;13:701–712. doi: 10.1038/nrn3346 PMID: 22968153.

45. O'Riordan K.J., Collins M.K., Moloney G.M., Knox E.G., Aburto M.R., Fülling C., Morley S.J., Clarke G., Schellekens H., Cryan J.F. Short chain fatty acids: Microbial metabolites for gut-brain axis signaling. Mol. Cell. Endocrinol. 2022;546:111572. doi: 10.1016/j.mce.2022.111572 PMID: 35066114.

46. Mirzaei R., Bouzari B., Hosseini-Fard S.R., Mazaheri M., Ahmadyousefi Y., Abdi M., Jalalifar S., Karimitabar Z., Teimoori A., Keyvani H., et al. Role of microbiota-derived short-chain fatty acids in nervous system disorders. Biomed. Pharmacother. 2021;139:111661. doi: 10.1016/j.biopha.2021.111661 PMID: 34243604.

47. Banasiewicz T., Domagalska D., Borycka-Kiciak K., Rydzewska G. Determination of butyric acid dosage based on clinical and experimental studies—A literature review. Prz. Gastroenterol. 2020;15:119–125. doi: 10.5114/pg.2020.95556 PMID: 32550943 PMCID: PMC7294979.

48. Wong K., Noubade R., Manzanillo P., Ota N., Foreman O., Hackney J.A., Friedman B.A., Pappu R., Scearce-Levie K., Ouyang W. Mice deficient in NRROS show abnormal microglial development and neurological disorders. Nat. Immunol. 2017;18:633–641. doi: 10.1038/ni.3743 PMID: 28459434.

49. Sarubbo F., Cavallucci V., Pani G. The Influence of Gut Microbiota on Neurogenesis: Evidence and Hopes. Cells. 2022;11:382. doi: 10.3390/cells11030382 PMID: 35159192 PMCID: PMC8834402.

50. Tang W., Meng Z., Li N., Liu Y., Li L., Chen D., Yang Y. Roles of gut microbiota in the regulation of hippocampal plasticity, inflammation, and hippocampus-dependent behaviors. Front. Cell. Infect. Microbiol. 2021;10:611014. doi: 10.3389/fcimb.2020.611014 PMID: 33585279 PMCID: PMC7873527.

51. Doroszkiewicz J, Groblewska M, Mroczko B. The Role of Gut Microbiota and Gut-Brain Interplay in Selected Diseases of the Central Nervous System. Int J Mol Sci. 2021 Sep 17;22(18):10028. doi: 10.3390/ijms221810028. PMID: 34576191; PMCID: PMC8471822.

52. Bachmann S. Epidemiology of Suicide and the Psychiatric Perspective. IJERPH. 2018;15:1425. doi: 10.3390/ijerph15071425 PMID: 29986446 PMCID: PMC6068947.

53. Smith K. Mental health: A world of depression. Nature. 2014;515:180–181. doi: 10.1038/515180a PMID: 25391942.

54. Maurer D.M., Raymond T.J., Davis B.N. Depression: Screening and Diagnosis. Am. Fam. Physician. 2018;98:508–515 PMID: 30277728.

55. Ghannoum MA, Ford M, Bonomo RA, Gamal A, McCormick TS. A Microbiome-Driven Approach to Combating Depression During the COVID-19 Pandemic. Front Nutr. 2021 Aug 24;8:672390. doi: 10.3389/fnut.2021.672390. PMID: 34504858; PMCID: PMC8421528.

56. Ruhé HG, Mason NS, Schene AH. Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. Mol Psychiatry. 2007 Apr;12(4):331-59. doi: 10.1038/sj.mp.4001949. Epub 2007 Jan 16. PMID: 17389902.

57. Carlessi AS, Borba LA, Zugno AI, Quevedo J, Réus GZ. Gut microbiota-brain axis in depression: The role of neuroinflammation. Eur J Neurosci. 2021 Jan;53(1):222-235. doi: 10.1111/ejn.14631. Epub 2019 Dec 18. PMID: 31785168.

58. Jiang H, Ling Z, Zhang Y, Mao H, Ma Z, Yin Y, Wang W, Tang W, Tan Z, Shi J, Li L, Ruan B. Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav Immun. 2015 Aug;48:186-94. doi: 10.1016/j.bbi.2015.03.016. Epub 2015 Apr 13. PMID: 25882912.

59. Aizawa E, Tsuji H, Asahara T, Takahashi T, Teraishi T, Yoshida S, Ota M, Koga N, Hattori K, Kunugi H. Possible association of Bifidobacterium and Lactobacillus in the gut microbiota of patients with major depressive disorder. J Affect Disord. 2016 Sep 15;202:254-7. doi: 10.1016/j.jad.2016.05.038. Epub 2016 May 24. PMID: 27288567.

60. Montagnani M, Bottalico L, Potenza MA, Charitos IA, Topi S, Colella M, Santacroce L. The Crosstalk between Gut Microbiota and Nervous System: A Bidirectional Interaction between Microorganisms and Metabolome. Int J Mol Sci. 2023 Jun 19;24(12):10322. doi: 10.3390/ijms241210322. PMID: 37373470; PMCID: PMC10299104.

61. Valles-Colomer M, Falony G, Darzi Y, Tigchelaar EF, Wang J, Tito RY, Schiweck C, Kurilshikov A, Joossens M, Wijmenga C, Claes S, Van Oudenhove L, Zhernakova A, Vieira-Silva S, Raes J. The neuroactive potential of the human gut microbiota in quality of life and depression. Nat Microbiol. 2019 Apr;4(4):623-632. doi: 10.1038/s41564-018-0337-x. Epub 2019 Feb 4. PMID: 30718848.

62. Huang R, Wang K, Hu J. Effect of Probiotics on Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2016 Aug 6;8(8):483. doi: 10.3390/nu8080483. PMID: 27509521; PMCID: PMC4997396.

63. Janik R, Thomason LAM, Stanisz AM, Forsythe P, Bienenstock J, Stanisz GJ. Magnetic resonance spectroscopy reveals oral Lactobacillus promotion of increases in brain GABA, N-acetyl aspartate and glutamate. Neuroimage. 2016 Jan 15;125:988-995. doi: 10.1016/j.neuroimage.2015.11.018. Epub 2015 Nov 11. PMID: 26577887.

64. Sampson TR, Mazmanian SK. Control of brain development, function, and behavior by the microbiome. Cell Host Microbe. 2015 May 13;17(5):565-76. doi: 10.1016/j.chom.2015.04.011. PMID: 25974299; PMCID: PMC4442490.

65. O'Mahony SM, Clarke G, Borre YE, Dinan TG, Cryan JF. Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. Behav Brain Res. 2015 Jan 15;277:32-48. doi: 10.1016/j.bbr.2014.07.027. Epub 2014 Jul 29. PMID: 25078296.

66. van de Wouw M, Boehme M, Lyte JM, Wiley N, Strain C, O'Sullivan O, Clarke G, Stanton C, Dinan TG, Cryan JF. Short-chain fatty acids: microbial metabolites that alleviate stress-induced brain-gut axis alterations. J Physiol. 2018 Oct;596(20):4923-4944. doi: 10.1113/JP276431. Epub 2018 Aug 28. PMID: 30066368; PMCID: PMC6187046.

67. Yu S, Wang L, Jing X, Wang Y, An C. Features of gut microbiota and short-chain fatty acids in patients with first-episode depression and their relationship with the clinical symptoms. Front Psychol. 2023 Apr 24;14:1088268. doi: 10.3389/fpsyg.2023.1088268. PMID: 37168424; PMCID: PMC10165121.

68. Peirce JM, Alviña K. The role of inflammation and the gut microbiome in depression and anxiety. J Neurosci Res. 2019 Oct;97(10):1223-1241. doi: 10.1002/jnr.24476. Epub 2019 May 29. PMID: 31144383.

69. Perrone MG, Centonze A, Miciaccia M, Ferorelli S, Scilimati A. Cyclooxygenase Inhibition Safety and Efficacy in Inflammation-Based Psychiatric Disorders. Molecules. 2020 Nov 18;25(22):5388. doi: 10.3390/molecules25225388. PMID: 33217958; PMCID: PMC7698629.

70. Keller J, Gomez R, Williams G, Lembke A, Lazzeroni L, Murphy GM Jr, Schatzberg AF. HPA axis in major depression: cortisol, clinical symptomatology and genetic variation predict cognition. Mol Psychiatry. 2017 Apr;22(4):527-536. doi: 10.1038/mp.2016.120. Epub 2016 Aug 16. PMID: 27528460; PMCID: PMC5313380.

71. Leucht S, Hierl S, Kissling W, Dold M, Davis JM. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. Br J Psychiatry. 2012 Feb;200(2):97-106. doi: 10.1192/bjp.bp.111.096594. PMID: 22297588.

72. Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, Nagler CR, Ismagilov RF, Mazmanian SK, Hsiao EY. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell. 2015 Apr 9;161(2):264-76. doi: 10.1016/j.cell.2015.02.047. Erratum in: Cell. 2015 Sep 24;163:258. PMID: 25860609; PMCID: PMC4393509.

73. Varesi A, Campagnoli LIM, Chirumbolo S, Candiano B, Carrara A, Ricevuti G, Esposito C, Pascale A. The brain-gut-microbiota interplay in depression: A key to design innovative therapeutic approaches. Pharmacol Res. 2023 Jun;192:106799. doi: 10.1016/j.phrs.2023.106799. Epub 2023 May 19. PMID: 37211239.

74. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, Biddinger SB, Dutton RJ, Turnbaugh PJ. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014 Jan 23;505(7484):559-63. doi: 10.1038/nature12820. Epub 2013 Dec 11. PMID: 24336217; PMCID: PMC3957428.

75. Berding K, Vlckova K, Marx W, Schellekens H, Stanton C, Clarke G, Jacka F, Dinan TG, Cryan JF. Diet and the Microbiota-Gut-Brain Axis: Sowing the Seeds of Good Mental Health. Adv Nutr. 2021 Jul 30;12(4):1239-1285. doi: 10.1093/advances/nmaa181. PMID: 33693453; PMCID: PMC8321864.

76. Parletta N, Zarnowiecki D, Cho J, Wilson A, Bogomolova S, Villani A, Itsiopoulos C, Niyonsenga T, Blunden S, Meyer B, Segal L, Baune BT, O'Dea K. A Mediterranean-style dietary intervention supplemented with fish oil improves diet quality and mental health in people with depression: A randomized controlled trial (HELFIMED). Nutr Neurosci. 2019 Jul;22(7):474-487. doi: 10.1080/1028415X.2017.1411320. Epub 2017 Dec 7. PMID: 29215971.

77. Varaee H, Darand M, Hassanizadeh S, Hosseinzadeh M. Effect of low-carbohydrate diet on depression and anxiety: A systematic review and meta-analysis of controlled trials. J Affect Disord. 2023 Mar 15;325:206-214. doi: 10.1016/j.jad.2022.12.030. Epub 2022 Dec 28. PMID: 36584702.

78. Li X, Zhang Q, Wang W, Yang ST. A Novel Inulin-Mediated Ethanol Precipitation Method for Separating Endo-Inulinase From Inulinases for Inulooligosaccharides Production From Inulin. Front Bioeng Biotechnol. 2021 Apr 29;9:679720. doi: 10.3389/fbioe.2021.679720. PMID: 33996788; PMCID: PMC8116588.

79. Peredo-Lovillo A, Romero-Luna HE, Jiménez-Fernández M. Health promoting microbial metabolites produced by gut microbiota after prebiotics metabolism. Food Res Int. 2020 Oct;136:109473. doi: 10.1016/j.foodres.2020.109473. Epub 2020 Jun 25. PMID: 32846558.

80. You S, Ma Y, Yan B, Pei W, Wu Q, Ding C, Huang C. The promotion mechanism of prebiotics for probiotics: A review. Front Nutr. 2022 Oct 5;9:1000517. doi: 10.3389/fnut.2022.1000517. PMID: 36276830; PMCID: PMC9581195.

81. Wang X, Zhang P, Zhang X. Probiotics Regulate Gut Microbiota: An Effective Method to Improve Immunity. Molecules. 2021 Oct 8;26(19):6076. doi: 10.3390/molecules26196076. PMID: 34641619; PMCID: PMC8512487.

82. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci U S A. 2011 Sep 20;108(38):16050-5. doi: 10.1073/pnas.1102999108. Epub 2011 Aug 29. PMID: 21876150; PMCID: PMC3179073.

83. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, Morelli L, Canani RB, Flint HJ, Salminen S, Calder PC, Sanders ME. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014 Aug;11(8):506-14. doi: 10.1038/nrgastro.2014.66. Epub 2014 Jun 10. PMID: 24912386.

84. Salminen S, Collado MC, Endo A, Hill C, Lebeer S, Quigley EMM, Sanders ME, Shamir R, Swann JR, Szajewska H, Vinderola G. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. Nat Rev Gastroenterol Hepatol. 2021 Sep;18(9):649-667. doi: 10.1038/s41575-021-00440-6. Epub 2021 May 4. Erratum in: Nat Rev Gastroenterol Hepatol. 2021 Sep;18(9):671. doi: 10.1038/s41575-021-00481-x. Erratum in: Nat Rev Gastroenterol Hepatol. 2022 Aug;19(8):551. doi: 10.1038/s41575-022-00628-4. PMID: 33948025; PMCID: PMC8387231.

85. Ghorbani Z, Nazari S, Etesam F, Nourimajd S, Ahmadpanah M, et al. The Effect of Synbiotic as an Adjuvant Therapy to Fluoxetine in Moderate Depression: A Randomized Multicenter Trial. Arch Neurosci. 2018;5(2):e60507. https://doi.org/10.5812/archneurosci.60507.