Wydawnictwo UR 2023
ISSN 2544-1361 (online)
doi: 10.15584/ejcem.2023.4.23

http://www.ejcem.ur.edu.pl
European Journal of Clinical and Experimental Medicine
Eur J Clin Exp Med 2023; 21 (4): 887–895

REVIEW PAPER

The gut microbiota in development and treatment of depression

Natalia Wilczek [1], Julia Bogucka [1], Anna Brzyska [1], Wiktoria Sielwanowska [1], Bartłomiej Syzdoł [2], Halina Piecewicz-Szczęsna [1]

[1] Student Research Group at the Chair and Department of Epidemiology and Clinical Research Methodology, Medical University of Lublin, Lublin, Poland
[2] Department of Child Neurology, Medical University of Lublin, Lublin, Poland

ABSTRACT

Introduction and aim. Nowadays, almost 4% of people in the world suffer from depressive disorders, and the forecasts of further increase in incidence are alarming. The disease is debilitating and can lead to suicide, and available treatments are still imperfect. The aim of the study was to review the literature and present the potential role of the gut microbiota in the development of depression and to consider the use of prebiotics and probiotics as one of the therapeutic options in this disease.

Material and methods. Review of articles published on PubMed since 2015.

Analysis of the literature. The available reports point to a relationship between disturbances in the composition of the intestinal flora and the development of depressive disorders. In addition, more and more studies indicate the benefits of the influence on mood and clinical improvement, observed when using psychobiotics as an adjuvant treatment of depression, as well as monotherapy.

Conclusion. Further research is needed in this area, especially in humans, to gain a deeper understanding of the role of the gut microbiota in depression and the promising use of psychobiotics for its treatment.

Keywords. depression, gut microbiota, microbiome-gut-brain axis, prebiotics, psychobiotics

Introduction

Around 3,8% of the human population worldwide currently suffer from depression, and this disease affects women by approximately 50% more than men.[1] Unfortunately, the problem is constantly increasing, and the most important and dangerous complication of this debilitating disease is the occurrence of suicides. Annually 700,000 people commit suicide in the world, and in the group of people 15–29 years old it is the 4th leading cause of death.[1] Currently, depression is the fourth most serious disease and according to forecasts by the World Health Organization, will be the most widespread disease entity by 2030.[2] The clinical picture of the disease mainly consists of low mood, anhedonia and cognitive disorders. Concentration problems may also occur, and sleep and eating are disturbed, which can disrupt the daily functioning of such a patient.[3] Despite the existence of many therapeutic options, the waiting time for the treatment effect is quite long, sometimes even up to 6 weeks. Moreover, recovery is not facilitated by the occurrence of side effects of these substances, which often forces clinicians to change treatment or add more medications to get the desired result.[4] It is estimated, that only half of the patients respond to treatment, and the diagnosis is made mainly on the basis of the symptoms reported by the patient, which means that the therapy is not specific to the pathophysiological mechanisms of depression.[5] Therefore, further progress is needed to better

Corresponding author: Natalia Wilczek, e-mail: natalia.wilczek09@gmail.com

Received: 24.08.2023 / Revised: 13.09.2023 / Accepted: 13.09.2023 / Published: 30.12.2023

Wilczek N, Bogucka J, Brzyska A, Sielwanowska W, Syzdoł B, Piecewicz-Szczęsna H. The gut microbiota in development and treatment of depression. *Eur J Clin Exp Med*. 2023;21(4):887–895. doi: 10.15584/ejcem.2023.4.23.

understand the pathophysiological mechanisms of this disease and to improve its treatment.[6] This is very important because there are a number of causative factors that can lead to depressive symptoms, including biological, genetic, environmental and psychological factors.[7] Increasingly, the influence of the state of the intestinal flora is considered as contributing to the development of this disease. Endogenous microbial intestinal flora, which consists of trillions of microorganisms, plays a key role in maintaining the correctness of physiological processes occurring in the human body.[8] Thanks to the presence of effective two-way communication between the intestines and the brain, based on numerous mechanisms, it is possible to mutually transfer the essential information between the aforementioned structures necessary for their proper functioning. This correlation is referred to as the microbiome-gut-brain axis (MGBA).[9] In recent years, researchers have shown increased interest in both the composition of this ecosystem and the potential associations of microbiome disorders with the occurrence of psychiatric or neurological diseases.[8] In addition, due to the search for new therapeutic options, attention is drawn to the effect of supplementation of probiotics, prebiotics and synbiotics on the clinical improvement of patients with depressive disorders.[10]

Aim

The aim of this review is to highlight the importance of the problem of depression and to present the role of the intestinal microbiota in its pathomechanism, and in addition to consider whether probiotics and prebiotics can be one of the therapeutic options for this disorder.

Material and methods

This review article focuses on on the role played by the intestinal microbiota in the pathomechanism of depression, and, on the other hand, consider the potential benefits using probiotics and prebiotics in terms of clinical improvement in people with depression, based on a selective review of PubMed publications. We have considered reviews and original papers since 2015 and WHO report.

Analysis of the literature

The microbiome-gut-brain axis

The mammalian gastrointestinal tract, including humans, is inhabited by nearly 1000-1500 species of bacteria. Together with various fungal and viral species, they constitute the gut microbiota, a diverse and variable community. This composition is influenced by factors such as diet, age, lifestyle, and inflammatory status.[11] A stable and diverse microbiota plays a crucial role in regulating metabolic and immune processes within the human body.[12] In recent years, scientists have discovered a bidirectional communication between the gut microbiota and the brain, termed the gut microbiota-brain axis. It means that the state of the gut microbiota influences the behavior and function of the brain, and the brain, through its many neural properties, influences gut function.[13] The specific mechanisms and connections within the gut microbiota-brain axis are very complex and not yet fully elucidated, and further research is needed to unravel the complexities of these interactions and correlations.[13,14] There are reports that these two areas of our body are connected by several ways, including nervous, hormonal, metabolic and immunological, including mainly the autonomic nervous system (ANS), the enteric nervous system (ENS), vagus nerve, the hypothalamic-pituitary-adrenal axis (HPA), the sympatho-adrenal system, and descending monoaminergic pathways.[15,16] The extensive connections between the nervous and gastrointestinal systems explain the potential presence of depressive and anxiety disorders in individuals with abnormal gut microbiota composition.[17] Changes in the gut microbiota composition can also impact the nervous system through metabolic pathways. Microorganisms in our intestines are capable of producing neurotransmitters such as dopamine, GABA, noradrenaline, short-chain fatty acids (SCFAs) and serotonin that affect the proper functioning of the brain and mood.[15,18-20] Neurotransmitters that are produced in abnormal amounts by the intestinal microflora can affect the development of neurological and depressive disorders.[19,20] For example, certain bacterial strains such as *Escherichia* spp. and *Lactobacillus* spp. can synthesize gamma-aminobutyric acid (GABA), which is an inhibitory neurotransmitter in the central nervous system.[18] Neurotransmitters such as kynurenine and serotonin also play a key role in the pathogenesis of depressive disorders. They are synthesized in the process of tryptophan metabolism, so a decrease in their level is most often associated with a decrease in the supply of this amino acid because it is obtained only from diet. Studies have shown that a diet increasing tryptophan levels can result in fewer depressive symptoms, while a diet low in this amino acid caused irritability and anxiety.[21] By also assessing the 3HKYN:KYN ratio, the level of destabilization can be estimated. This coefficient reflects the degree of conversion of kynurenines via the kynurenine pathway. Disturbances in kynurenine metabolism are reflected in a wide range of somatic and psychiatric diseases.[22] In addition, the vagus nerve plays a crucial role in maintaining the continuity of proper MGBA communication. Microorganisms regulate the activation of the vagus nerve, and then the signal is transmitted to the CNS, enabling healthy mental functioning. It is therefore assumed that disturbances in the composition of the intestinal ecosystem can affect the information transmitted to the brain via the vagus nerve, and

in consequence causing the symptoms of depression.[23] Each change in the composition of the intestinal microbiome causes the production of lipopolysaccharides (LPS) by microorganisms, which results in the activation of inflammatory reactions. The cytokines produced send signals to the vagus nerve, thus connecting to the HPA axis. There are reports suggesting that cutting the nerve X caused the disappearance of the influence of the microbiome on the behavior of animals tested for anxiety and depression symptoms.[24] The hormonal regulation of MGBA is mainly based on the HPA axis pathway. The intestinal microflora regulates the proper functioning of the HPA, for which it is responsible already in the first years of life. Numerous reports have shown that excessive activity in the HPA area is important for the development of depression, e.g. through excessive activity of adrenocorticotropic hormone (ACTH), corticotropin-releasing hormone (CRH) and cortisol, which disturbs appropriate the body's response to psychological stress.[25] There are also reports suggesting a potential influence of the gut microbiota through Toll-like receptors 2 and 4 (TLR2 and TLR4).[16] Disruptions in the gut microbiota composition can compromise the integrity of the gut barrier, leading to increased permeability. This can result in the translocation of bacterial metabolites to mesenteric lymphoid tissues, potentially contributing to neurological disorders.[26] A prominent component of the gut microbiota, LPS, is recognized by Toll-like receptors mainly located on microglial cells. This activation leads to the release of pro-inflammatory cytokines, contributing to the development of neurological disorders.[27] These and many other mechanisms, not fully understood, contribute to the bidirectional relationship between the gastrointestinal and nervous systems known as the gut microbiota-brain axis. Changes in the composition of gut microbiota can lead to alterations in immune regulation and metabolic changes that influence the nervous system. Imbalance in the MGBA contributes to the development of many diseases, particularly depression and anxiety disorders.[28]

The potential impact of gut microbiota in the development of depression

In recent years, numerous studies have been conducted comparing the gut microbiota composition of individuals with depression and anxiety disorders to control groups. A consistent trend has been observed, showing an increase in the abundance of bacteria from the *Bacteroidetes, Protobacteria*, and *Actinobacteria genera*, as well as a decrease in the abundance of bacteria from the *Firmicutes genus* in patients with depressive and anxiety disorders. Additionally, reduced levels of bacteria from the *Faecalibacterium*, *Eubacterium rectale, Lachnospira, Butyricicoccus,* and *Sutterella* genera in individuals with depressive and anxiety disorders result in decreased production of short-chain fatty acids (SCFA).[29] Consequently, this leads to disruption of the gut barrier and dysregulation of the immune system, which impacts brain dysfunction.[29,30] Fecal samples of Polish women were analyzed for the presence of SCFA in order to investigate the role of this factor as a potential cause of women's mental health disorders. In the group of 11 patients who did not show depressive symptoms, higher concentrations of almost all short-chain fatty acids were observed compared to the group of patients who were diagnosed with worsening depression using the Beck Depression Inventory (BDI). Moreover, in the group of women who showed depressive symptoms, increased levels of isocaproic acid were observed, which may contribute to the development of these symptoms.[31] In many other studies comparing the gut microbiota composition of individuals with depression and anxiety disorders, a decreased level of bacteria from the *Prevotella* genus has been demonstrated compared to the control group.[32-35] Individuals with depression and anxiety disorders have also been observed to have a lower abundance of bacteria from the *Faecalibacterium* and *Sutterella genera*.[34] Furthermore, the presence of bacteria from the *Eggerthella* genus has been positively correlated with the occurrence of depressive and anxiety disorders.[33] Patients suffering from depression are often accompanied by intestinal disorders such as vomiting, abdominal pain, constipation, nausea, bloating or even irritable bowel syndrome (IBS).[36] It has been proven that the presence of disturbances in the composition of the intestinal microbiota may affect mood disorders. The meta-analysis showed that patients suffering from major depressive disorder (MDD) in the composition of their intestinal microbiota have less bacteria from the families: *Veillonellaceae*, *Prevotellaceae* and *Sutterellaceae* and less bacteria from the genus: *Coprococcus*, *Faecalibacterium*, *Ruminococcus*, *Bifidobacterium* and *Escherichia* compared to healthy subjects. In patients with depressive disorders there was an increased level of bacteria of the genus *Paraprevotella.*[37] Other scientific work has shown that the following are involved in the pathogenesis of depression: increased number of *Enterobacteriaceae* and *Alistipes* bacteria and decreased number of *Faecalibacterium*. What's more, anxiety and depression were accompanied by the presence of bacteria from the families: *Ruminococcaceae*, *Shewanellaceae*, *Halomonadaceae* and *Verrucomicrobiae*. A clinical study found elevated numbers of *Bacteroidetes* and *Proteobacteria* in MDD patients and decreased numbers of the *Lachnospiraceae* and *Ruminococcaceae* families.[36] Studies conducted on rodents have proven that animals exhibiting depressive behavior had a higher ratio of *Bacteroides* to *Firmicutes* bacteria in their gut microbiota. An experiment with mice exposed to chronic stress showed an increased population of *Clostridium* and a decreased

population of *Bacteroides* in their gut microbiota. Observing these relationships prompted scientists to look for biological relationships between intestinal dysbiosis and the occurrence of depression. It has been proven that changes in the intestinal microflora are associated with a change in the permeability of the intestinal barrier and with chronic inflammation. Modifications in the permeability of the intestinal barrier occur by reducing the number of strict proteins: claudin-5 and occludin. This is associated with changes in the secretion of intestinal peptides that have the ability to contact the central nervous system, taking a part in the gut-brain axis.[37] Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis is also associated with leaky gut. HPA stimulates the immune system and the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS and RNS can damage structures in cell membranes, causing leaky gut and chronic inflammation. Factors that activate the HPA axis include LPS, secreted by Gram-negative bacteria, and peptidoglycan, a component of the cell wall of most bacteria. Hyperactivation of HPA increases the secretion of cortisol, the high level of which can cause depression. Homocysteine is an amino acid synthesized from the breakdown of folic acid, vitamin B6 and vitamin B12. Scientific studies have shown that increased levels of homocysteine are associated with depression. Hyperhomocysteinemia disrupts the epithelial barrier and causes increased intestinal permeability, which causes inflammation. It has been proven that the bacteria that are the main producers of this amino acid are: *Subdoligranulum* sp., *Eubacterium* sp. and *Clostridiales* family XIII.[36] Gram-negative bacteria present in the intestines secrete endotoxin-lipopolysaccharide (LPS), which triggers the production of post-inflammatory cytokines such as: IL-6, IL-1β and TNF-α, contributing to the abnormal secretion of intestinal peptides and thus the pathological functioning of the intestinal-gut axis cerebral. Increased amount of the pro-inflammatory enzyme indoleamine 2,3-dioxygenase, secreted e.g. as a result of the action of LPS, reduces the level of serotonin, the deficiency of which is crucial in the development of depression.[36,37] In addition, intestinal dysbiosis triggers the loss of goblet cells, which results in a reduction in mucus secretion and thinning of its' layer. This may be the reason why toxic metabolites move into the bloodstream and cause inflammation.[36] Yuan et al. conducted an analysis of gut microbiota in 240 study participants, among whom 129 were suffering from active colitis ulcerosa (CU). In patients with coexisting depression and CU, a lower diversity of gut microbiota was observed compared to patients with UC without depression. Furthermore, individuals with both CU and depression exhibited a microbiota composition characterized by a reduced abundance of bacteria from the *Prevotella and Lachnospira* genus, along with an increased overgrowth of bacteria from the *Lactobacillales, Sellimonas, Streptococcus*, and *Enterococcus genera*, as compared to those with CU but without depressive disorders.[38] Depression and dementia are the most common diseases diagnosed in the elderly. Malnutrition is a massive problem in the geriatric population, which may be a cause of depression and may also exacerbate its symptoms. Depressive disorders in the elderly are associated with weakness, worse outcomes of chronic diseases and even higher mortality. A review of scientific articles proved that an adequate supply of nutrients has a positive effect on the occurrence of depression in this age group. Omega-3 fatty acid supplementation reduces oxidative stress, which is associated with depressive symptoms. In addition, fasting has a positive effect on the brain availability of serotonin, the deficiency of which is closely related to the disease. It has been proven that a low-calorie diet with the preservation of protein, minerals, water and vitamins also has a positive effect on well-being.[39] Depressive disorders are diagnosed twice as often in women. This is due to fluctuations in estradiol levels. Physiological decline in the level of this hormone occurs after menopause and after childbirth. Pathological causes include ovarian failure, hyperprolactinemia, congenital adrenal hyperplasia, and polycystic ovary syndrome. A scientific study aimed to detect microbes that break down estradiol in the intestines of women with depression in premenopausal age. Initially, estradiol was incubated with intestinal microbes taken from women suffering from depression and from healthy patients. It was found that this hormone decomposes within 120 minutes in 77.8% of women suffering from depression and in 19.3% of women without depression. Then it was established that the bacterium that degrades estradiol is *Klebsiella aerogenes* by the enzyme 3β-hydroxysteroid dehydrogenase (3β-HSD). Other bacteria that were detected in patients with the 3β-HSD enzyme were: *Bacteroides thetaiotaomicron* and *Clostridia*.[40] Diet also plays an important role in the proper functioning of the intestinal microbiota. It has been observed that individuals following a healthy and balanced diet are less prone to depression. Research conducted on the impact of diet on gut microbiota composition indicates that a low-fiber diet rich in saturated fats reduces the levels of bacteria from the Lactobacilli genus. On the other hand, the mediterranean diet reduces the number of pathogenic bacteria such as Escherichia coli, and increases the abundance of key commensal bacteria like *Bifidobacteria*, *Clostridium cluster* XVIa and *Faecalibacterium prausnitzii*.[9]

The use of probiotics and prebiotics as a potential therapeutic option for depression

Increasingly, the modification of the intestinal microbiota with the use of supplementation with probiotic

or prebiotic substances is being considered. Over the last decade, the concept of psychobiotics has appeared, which is defined as probiotic bacteria that, when used in appropriate doses, have an effect on the function of the intestinal microbiota and MGBA, contributing to the improvement of mental health.[24] Potential properties are attributed mainly to substances containing strains of bacteria from the Lactobacillus, Bifidobacterium, Streptococcus and Enterococcus groups. When it comes to prebiotics, these are food elements that have not been digested and thus contribute to the stimulation of growth and activity of bacteria in our intestines.[41] Eight-week study conducted on a group of 110 patients, of whom 81 with abnormal depressive symptoms, who were randomly assigned to the one of groups using prebiotic, probiotic or placebo. The therapeutic effect was compared by patients‘ subjective assessment of the severity of the effect using the BDI. It was observed that, compared to the use of placebo,benefits were incurred in connection with the use of a probiotic (*Lactobacillus helveticus and Bifidobacterium longum*), and in the case of a prebiotic (galactooligosaccharide) no effect on improving the well-being of the patients.[42] A post hoc analysis showed an improvement in the antidepressant response in depressed subjects who took the probiotic substance *L. helveticus* R0052 and *B. longum* R0175, compared to the groups using placebo and prebiotic. In addition, in this study assessed the level of neurotrophin, the deficiency of which may disturb the physiological processes of the central nervous system, and, according to recent reports, also contribute to the occurrence of mood disorders and symptoms of depression. There was a significant increase in BDNF due to the probiotic, and interestingly, a slight decrease in BDNF was observed in the prebiotic group. Further research is recommended to examine the impact of the use of psychobiotics and prebiotics on the level of BDNF and the correlation of this factor with the severity of depressive symptoms.[43] In another study, the effectiveness of the use of a probiotic containing Clostridium butyricum MIYAIRI 588 was tested and clinical improvement was demonstrated in 70% of the subjects, where the probiotic was used as a supportive treatment in therapy, without observing any disturbing side effects.[44] The use of probiotics as adjuvant treatment was also evaluated by Rudzki et al., who in a randomized study assigned patients to two groups, the first received a probiotic containing *Lactobacillus plantarum* 299v (LP299v) and an SSRI for eight weeks, and the second group received an SSRI and placebo. On a weekly basis, the severity of the symptoms of the disease and cognitive processes were assessed using the available depression scales, and what is more, biochemical tests were carried out, taking into account, among others, the level of tryptophan and kynurenine. In the group of people using a probiotic and antidepressant treatment, a significant improvement in cognitive processes was noticed, and what is more, a decrease in the concentration of kynurenine, i.e. a substance that under physiological conditions has a neuroprotective effect, was observed, and its high concentrations determine neurodegenerative and neurotoxic processes.[45] Another study also showed a positive effect of the use of probiotics in the treatment of depressive disorders. Patients were treated once with *Lactobacillus acidophilus, Lactobacillus casei and Bifidobacterium bifidum*. Patients suffering from depression and receiving probiotics achieved an improvement in their health condition (assessment according to the BDI questionnaire) compared to patients who received placebo.[46] In recent years, attempts have also been made to treat major depressive disorders using *Lactobacillus casei* strain Shirota (LcS). In a study involving patients with major depressive disorders, a decrease in the severity of depression symptoms based on the Hamilton Depression Rating Scale was observed after using the above-mentioned probiotic. These changes correlated with a change in the composition of the intestinal microbiota, which is crucial in the treatment of depressive disorders.[47] There is a need to conduct further studies to confirm the effectiveness of using probiotics in combination with antidepressants in patients with depression.[44-47] The use of a probiotic as the only therapeutic option for depression was considered by Wallace and Milev and conducted an open-label pilot study on a group of patients with major depressive disorder (MDD) who had not previously received treatment for major depressive disorder. 70% of the respondents were women. During the 8-week study period, patients took a probiotic once a day consisting of *L. helveticus* R0052 (90%) and *B. longum* R0175 (10%). Available clinical scales and self-report questionnaires were used to assess the effectiveness of treatment. Significant improvement in the area of symptoms was observed in the patients, as well as a reduction in the sense of anxiety after both 4 and 8 weeks, and in addition, the subjectively assessed quality of sleep significantly improved in the 8th week of the study. The use of the above probiotic was not associated with side effects and was well tolerated by patients. However, due to the fact that the study was conducted on a relatively small group of people, there is a need to conduct randomized, comprehensive studies on a larger number of people in order to justify the effectiveness of using probiotic substances as monotherapy in the treatment of depressive disorders.[48] The effectiveness of probiotic use was assessed in patients with various the composition of the microbiotawith various severity of depressive disorders. A placebo control was applied over an 8-week period, and compared the symptoms and composition of the ecosystem present in the intestines with a group of people who did not suffer from depression. It was noted that

Table 1. Clinical evaluation of probiotics on depression*

Strains	Population characteristics	Intervention	Duration	Clinical findings	Use of antidepressants	References
L. casei strain Shirota (LcS)	15 patients with MDD and 3 patients with BD	160 mL fermented milk containing at least 8.0×10^{10} CFU of LcS per day	12 weeks	↓HAMD - 17 0 weeks 17.7 ± 4.1, 12 weeks 10.9 ± 7.3) ↑ Bifidobacterium, Actinobacteria phylum	yes	Otaka et al., 2021.[47]
L. acidophilus , *L. casei, B. bifidum*	40 patients with MDD Probiotics (n=20) Placebo (n=20)	Oral capsule contained 2×10^9 CFU/g *L. acidophilus*, 2×10^9 CFU/g *L. casei*, 2×10^9 CFU/g *B. bifidum* per day	8 weeks	↓ BDI Probiotics(-5.7±6.4) placebo (-1.5±4.8)	yes	Akkasheh et al., 2015.[46]
Probiotics: *L. helveticus, B. longum*, Prebiotics: galactooligosaccharide	81 patients with MDD Probiotics (n=28) Prebiotics (n=27) Placebo (n=26)	Probiotics: 10 x 10^9 CFU per 5g sachet/day Prebiotics: galactooligosaccharide sachet/day	8 weeks	↓ BDI (probiotics 17.39-9.1), prebiotics (19.72-14.14), (placebo 18.18-15.55) ↓ kynureine/tryptophan ↑ tryptophan/isoleucine	yes	Kazemi et al., 2018.[42]
L. helveticus R0052, *B. longum* R0175 Prebiotics: galactalogosaccharide	78 patients with MDD Probiotic (n=28) Prebiotic (n=25) Placebo, (n=25)	Probiotics: ≥ 10×10^9 CFU *L. helveticus* R0052 and *B. longum* R0175 per 5 g sachet/day Prebiotics: galactalogosaccharide sachet	8 weeks	↑ BDNF (the biggest increase in probiotic group) ↓ BDI (probiotics 17.6 -9.8), (prebiotics 19.7- 14.1), (placebo 18.2-15.9)	yes	Heidarzadeh-Rad et al., 2020.[43]
C. butyricum MIYAIRI 588 (CBM588)	40 patients with MDD Probiotics (n=20) Placebo (n=20)	60 mg/d of *C. butyricum* CBM588 oraly per day	8 weeks	↓ HAMD-17, BDI, BAI (Probiotics: decrease 50% or greater)	yes	Miyaoka et al., 2018.[44]
L. plantarum 299v (LP299v)	60 patients with MDD Probiotics (n=30) Placebo (n=30)	2 capsules per day (each capsule contained 10x10^9CFU of L. Plantarum 299v)	8 weeks	↓ HAMD-17, SCL-90 and PSS-10 ↓ KYN (Probiotics 2,05-1,82), (Placebo 2,17-2,32) ↑ 3HKYN:KYN (Probiotics 15.88-27.68), (placebo 17.82 -15.26)	yes	Rudzki et al., 2019.[45]
L. helveticus R0052, *B. longum* R0175	10 patients with MDD	3×10^9 CFU of *L. helveticus* R0052 and *B. longum* R0175 per day	8 weeks	↓ MADRS (24.9 - 12.7), QIDS-SR16 (20.5 - 11.6), SHAPS (36.8-30.7)	no	Wallace et al., 2021.[48]
B. bifidum W23, *B. lactis* W51, *B. lactis* W52, *L. acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, *Lactococcus lactis* W19 and *L. lactis* W58	71 patients with depression syndromes Probiotics (n=34) Placebo (n=37)	Ecologic®Barrier 2.5×10^9 CFU/g *B. bifidum* W23, *B. lactis* W51, *B. lactis* W52, *L. acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, *L. lactis* W19 and *L. lactis* W58 2g per day	8 weeks	↓ BDI (Probiotics 28.91- 19.88) (placebo 27.97- 19.25)	yes	Chahwan et al., 2019.[49]
B. bifidum W23, *B. lactis* W51, *B. lactis* W52, *L. acidophilus* W22, *L. casei* W56, *L. paracasei* W20, *L. plantarum* W62, *L. salivarius* W24, *L. lactis* W19	61 patients with depression syndoms Probiotics (n=28) Placebo (n=33)	3g Omnibiotic Stress Repair® 7,5 x 109 CFU of *B. bifidum* W23, *B. lactis* W51, *B. lactis* W52, L. acidophilus W22, *L. casei* W56, *L. paracasei* W20, *L. plantarum* W62, *L. salivarius* W24 and *L. lactis* W19	28 days	↑ *Ruminococcus gauvreauii*, *Coprococcus* 3 (Probiotics group)	yes	Reininghaus et al., 2020.[50]

* MDD – major depressive disorder, HAMD–17 – Hamilton Depression Rating Scale, BDI – Beck Depression Inventory, BAI – Beck Anxiety Inventory, BDNF – brain–derived neurotrophic factor, SCL–90 – Symptom Checklist; PSS–10 – Perceived Stress Scale, KYN – kynureine 3HKYN:KYN – 3–hydroxykynurenine: kynureine, MADRS – Montgomery-Åsberg Depression Rating Scale,QIDS–SR16 – Quick Inventory of Depressive Symptomatology, SHAPS – Snaith–Hamilton Pleasure Scale

the use of probiotic substances – Ecologic® Barrier significantly improved cognitive functions compared to patients using placebo, but changes in microbiota were not so marked.[49] In people hospitalized with severe depressive episodes, there was an increase in the number of *Ruminococcus gauvreauii* and *Coprococcus* 3, which are perceived as potentially beneficial bacteria for the functioning of the human body, after treatment with probiotic with biotin compared to the control group that received biotin with biotin. The study confirms that the use of probiotic substances contributes to beneficial changes in the composition of the intestinal microbiota, already in the first weeks of treatment, in patients with major depressive disorders. There are reports that suggest that probiotics are effective in terms of balancing the composition of this ecosystem which prompts further considerations.[50] Much less research assesses the effect of prebiotics on the severity of depressive symptoms, and current reports suggest a rather small effect in the treatment of these disorders. However, there is a need to increase the research base that focuses on prebiotics in this aspect.[51] The results of studies on the use of probiotics in the treatment of depression are summarized in detail in Table 1. below, taking into account the

duration of the study, the composition and dose of probiotics used, changes in parameters assessing the therapeutic effect, characteristics of the study population and whether the patients were undergoing antidepressant treatment at the same time.

Depression is a disease entity that often poses a great diagnostic challenge among specialists, especially in the first phase of the disease. Disturbing forecasts regarding the increase in incidence, which may also result in an increase in the number of suicides as a result of it, indicate the need for a deeper understanding of many poorly understood mechanisms that can cause depression.[1-3] Recently, the interest of researchers has focused on the importance of the brain-gut microbiota axis, e.g. in terms of interactions on proper functioning through numerous mechanisms, including neuronal, hormonal or immunological pathways. Dysfunction within the composition of the intestinal ecosystem may contribute to a negative impact on the brain, which in turn may contribute to mood disorders and the appearance of a depressive episode.[25] Existing reports suggesting the influence of the microbiota on the regulation of brain functions as well as its impact on behavior and mood encourage further research that will go even deeper into determining the qualitative and quantitative changes in the microbiome in depressed patients as opposed to healthy people.[15] In patients with depressive disorders, changes in the composition of the intestinal microbiota were demonstrated, manifested by an increase in the population of *Bacteroidetes, Protobacteria, Enterobacteriaceae, Alistipes and Actinobacteria*, and a decrease in the share of strains of the genus *Firmicutes, Faecalibacterium, Eubacterium rectale, Lachnospira*, *Butyricicoccus, Prevotella and Sutterella*.[29-37] The observation of changes in the intestinal microbiota in patients with depressive disorders prompts further observations and expanding the existing knowledge on this subject. Therefore, attempts are made to modify this composition so as to alleviate depressive symptoms, which is why further research conducted with the use of psychobiotic supplementation is crucial to be able to use these substances as one of the therapeutic options or for supportive treatment with antidepressants.[42-50] In addition, it is worth paying more attention to prebiotics and testing them in terms of treating depression, because the current literature presents very few reports on this subject.[51] Further research and reports in this area will help to better understand the role of intestinal microbiota in the pathomechanism of depression, and on the other hand also its beneficial effect in the treatment of these disorders.

Conclusion

Disturbances in the composition of the intestinal microbiota may predispose to depression, but further research is needed in this area, especially with the participation of humans, which will allow for a deeper understanding of the role of this causative factor in the pathophysiology of depression. In addition, the use of an appropriate, well-balanced diet as well as the supplementation of probiotic and prebiotic substances, which can have a positive effect on balancing the composition of the intestinal microbiota and contribute to the clinical improvement of patients with depression. It is therefore encouraged to continue further research, as modifying the composition of the ecosystem in our intestines may be a potentially promising therapeutic option for a disease that is a threat to civilization, i.e. depression.

Declarations

Funding

This research received no external funding.

Author contributions

Conceptualization, N.W., W.S. and A.B.; Validation, N.W., W.S., A.B. and J.B.; Resources, A.B., J.B. and B.S.; Data Curation, N.W., B.S. and J.B.; Writing – Original Draft Preparation, N.W., W.S., A.B., J.B. and B.S.; Writing – Review & Editing, N.W., W.S., J.B., A.B. and B.S.; Supervision, H.P.C.; Project Administration, N.W. and H.P.C.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

Not applicable.

References

1. World Health Organization. Depressive Disorder (Depression). World Health Organisation. https://www.who.int/news-room/fact-sheets/detail/depression. Published March 31, 2023. Accessed July 28, 2023.
2. Depression – Metaphorical Therapy. https://metaphoricaltherapy.com/problems/depression/. Accessed July 28, 2023.
3. Dobrek L, Głowacka K. Depression and Its Phytopharmacotherapy – A Narrative Review. *Int J Mol Sci*. 2023;24(5):4772. doi: 10.3390/ijms24054772
4. Marwaha S, Palmer E, Suppes T, Cons E, Young AH, Upthegrove R. Novel and emerging treatments for major depression. *Lancet.* 2023;14;401(10371):141-153. doi: 10.1016/S0140-6736(22)02080-3
5. Ménard C, Hodes GE, Russo SJ. Pathogenesis of depression: Insights from human and rodent studies. *Neuroscience*. 2016;321:138-162. doi: 10.1016/j.neuroscience.2015.05.053
6. Simpson CA, Diaz-Arteche C, Eliby D, Schwartz OS, Simmons JG, Cowan CSM. The gut microbiota in anxiety and

depression – A systematic review. *Clin Psychol.* 2021;83: 101943. doi: 10.1016/j.cpr.2020.101943
7. Munro M, Milne R. Symptoms and causes of depression and its diagnosis and management. *Nursing Times*. 2020; 116:4-18.
8. Suganya K, Koo BS. Gut–Brain Axis: Role of Gut Microbiota on Neurological Disorders and How Probiotics/Prebiotics Beneficially Modulate Microbial and Immune Pathways to Improve Brain Functions. *Int J Mol Sci.* 2020;21(20):7551. doi: 10.3390/ijms21207551
9. Bear TLK, Dalziel JE, Coad J, Roy NC, Butts CA, Gopal PK. The Role of the Gut Microbiota in Dietary Interventions for Depression and Anxiety. *Adv Nutr.* 2020;11(4):890-907. doi: 10.1093/advances/nmaa016
10. Liu RT, Walsh RFL, Sheehan AE. Prebiotics and probiotics for depression and anxiety: A systematic review and meta-analysis of controlled clinical trials. *Neurosci Biobehav Rev*. 2019;102:13-23. doi: 10.1016/j.neubiorev.2019.03.023
11. Kim S, Jazwinski S Michal. The Gut Microbiota and Healthy Aging: A Mini-Review. *Gerontology*. 2018;64(6): 513-520. doi: 10.1159/000490615
12. Lynch SV, Pedersen O. The Human Intestinal Microbiome in Health and Disease. Phimister EG, ed. *Engl J Med*. 2016;375(24):2369-2379. doi: 10.1056/nejmra1600266
13. Martin CR, Osadchiy V, Kalani A, Mayer EA. The Brain-Gut-Microbiome Axis. *CMGH Cell Mol Gastroenterol.* 2018;6(2):133-148. doi: 10.1016/j.jcmgh.2018.04.003
14. Mayer EA. Gut feelings: the emerging biology of gut–brain communication. *Na Re Neurosci.* 2011;12(8):453-466. doi: 10.1038/nrn3071
15. Cox LM, Weiner HL. Microbiota Signaling Pathways that Influence Neurologic Disease. *Neurotherapeutics*. 2018;15(1):135-145. doi: 10.1007/s13311-017-0598-8
16. Heiss CN, Olofsson LE. The role of the gut microbiota in development, function and disorders of the central nervous system and the enteric nervous system. *J Neuroendocrinol.* 2019;31(5):e12684. doi: 10.1111/jne.12684
17. Yuan N, Chen Y, Xia Y, Dai J, Liu C. Inflammation-related biomarkers in major psychiatric disorders: a cross-disorder assessment of reproducibility and specificity in 43 meta-analyses. *Transl Psychiatry*. 2019;9(1):233. doi: 10.1038/s41398-019-0570-y
18. Auteri M, Zizzo MG, Serio R. GABA and GABA receptors in the gastrointestinal tract: from motility to inflammation. *Pharmacol Res*. 2015;93:11-21. doi: 10.1016/j.phrs.2014.12.001
19. Israelyan N, Del Colle A, Li Z, et al. Effects of Serotonin and Slow-Release 5-Hydroxytryptophan on Gastrointestinal Motility in a Mouse Model of Depression. *Gastroenterology*. 2019;157(2):507-521.e4. doi: 10.1053/j.gastro.2019.04.022
20. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites. *Cell*. 2016;165(6):1332-1345. doi: 10.1016/j.cell.2016.05.041
21. Correia AS, Vale N. Tryptophan Metabolism in Depression: A Narrative Review with a Focus on Serotonin and Kynurenine Pathways. *Int. J Mol. Sci.* 2022;23(15):8493. doi: 10.3390/ijms23158493
22. Aarsland TIM, Instanes JT, Posserud MBR, Ulvik A, Kessler U, Haavik J. Changes in Tryptophan-Kynurenine Metabolism in Patients with Depression Undergoing ECT—A Systematic Review. *Pharmaceuticals*. 2022;15(11):1439. doi: 10.3390/ph15111439
23. Winter G, Hart RA, Charlesworth RPG, Sharpley CF. Gut Microbiome and Depression: What We Know and What We Need to Know. Reviews in the neurosciences. *Rev Neurosci*. 2018;29(6):629-643. doi: 10.1515/revneuro-2017-0072.
24. Trzeciak P, Herbet M. Role of the Intestinal Microbiome, Intestinal Barrier and Psychobiotics in Depression. *Nutrients*. 2021;13(3):927. doi: 10.3390/nu13030927
25. Du Y, Gao XR, Peng L, Ge JF. Crosstalk between the microbiota-gut-brain axis and depression. *Heliyon*. 2020;6(6): e04097. doi: 10.1016/j.heliyon.2020.e04097
26. Tyler Patterson T, Grandhi R. Gut Microbiota and Neurologic Diseases and Injuries. *Adv Exp Med Biol*. 2020;1238:73-91. doi: 10.1007/978-981-15-2385-4_6
27. Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, Flier JS. TLR4 links innate immunity and fatty acid–induced insulin resistance. *J Clin Invest*. 2006;116(11):3015-3025. doi: 10.1172/jci28898
28. Chang L, Wei Y, Hashimoto K. Brain–gut–microbiota axis in depression: A historical overview and future directions. *Brain Res Bull.* 2022;182:44-56. doi: 10.1016/j.brainresbull.2022.02.004
29. Van de Wouw M, Boehme M, Lyte JM, et al. Short-chain fatty acids: microbial metabolites that alleviate stress-induced brain-gut axis alterations. *J Physiol*. 2018;596(20): 4923-4944. doi: 10.1113/jp276431
30. Peirce JM, Alviña K. The role of inflammation and the gut microbiome in depression and anxiety. *J Neurosci Res.* 2019;97(10):1223-1241. doi: 10.1002/jnr.24476
31. Capuco A, Urits I, Hasoon J, et al. Current Perspectives on Gut Microbiome Dysbiosis and Depression. *Adv Ther*. 2020;37(4):1328-1346. doi: 10.1007/s12325-020-01272-7
32. Chen Z, Li J, Gui S, et al. Comparative metaproteomics analysis shows altered fecal microbiota signatures in patients with major depressive disorder. *NeuroReport*. 2018;29(5):417-425. doi: 10.1097/wnr.0000000000000985
33. Chung YE, Chen HC, Chou HL, et al. Exploration of microbiota targets for major depressive disorder and mood related traits. *J Psychiatr Res.* 2019;111:74-82. doi: 10.1016/j.jpsychires.2019.01.016
34. Jiang H, Ling Z, Zhang Y, et al. Altered fecal microbiota composition in patients with major depressive disorder. *Brain Behav Immun.* 2015;48:186-194. doi: 10.1016/j.bbi.2015.03.016
35. Kelly JR, Borre Y, O' Brien C, et al. Transferring the blues: Depression-associated gut microbiota induces neurobe-

havioural changes in the rat. *J Psychiatr Res*. 2016;82:109-118. doi: 10.1016/j.jpsychires.2016.07.019

36. Sonali S, Ray B, Ahmed Tousif H, et al. Mechanistic Insights into the Link between Gut Dysbiosis and Major Depression: An Extensive Review. *Cells*. 2022;11(8):1362. doi: 10.3390/cells11081362
37. Młynarska E, Gadzinowska J, Tokarek J, et al. The Role of the Microbiome-Brain-Gut Axis in the Pathogenesis of Depressive Disorder. *Nutrients*. 2022;14(9):1921. doi: 10.3390/nu14091921
38. Yuan X, Chen B, Duan Z, et al. Depression and anxiety in patients with active ulcerative colitis: crosstalk of gut microbiota, metabolomics and proteomics. *Gut Microbes*. 2021;13(1). doi: 10.1080/19490976.2021.1987779
39. Klimova B, Novotny M, Valis M. The Impact of Nutrition and Intestinal Microbiome on Elderly Depression—A Systematic Review. *Nutrients*. 2020;12(3):710. doi: 10.3390/nu12030710
40. Li D, Sun T, Tong Y, et al. Gut-microbiome-expressed 3β-hydroxysteroid dehydrogenase degrades estradiol and is linked to depression in premenopausal females. *Cell Metab.* 2023;4;35(4):685-694.e5. doi: 10.1016/j.cmet.2023.02.017
41. Chudzik A, Orzyłowska A, Rola R, Stanisz GJ. Probiotics, Prebiotics and Postbiotics on Mitigation of Depression Symptoms: Modulation of the Brain–Gut–Microbiome Axis. *Biomolecules*. 2021;11(7):1000. doi: 10.3390/biom11071000
42. Kazemi A, Noorbala AA, Azam K, Eskandari MH, Djafarian K. Effect of probiotic and prebiotic vs placebo on psychological outcomes in patients with major depressive disorder: A randomized clinical trial. *Clin Nutr*. 2019;38(2):522-528. doi: 10.1016/j.clnu.2018.04.010
43. Heidarzadeh-Rad N, Gökmen-Özel H, Kazemi A, Almasi N, Djafarian K. Effects of a Psychobiotic Supplement on Serum Brain-derived Neurotrophic Factor Levels in Depressive Patients: A Post Hoc Analysis of a Randomized Clinical Trial. *Clin Neuropharmacol*. 2020;26(4):486-495. doi: 10.5056/jnm20079
44. Miyaoka T, Kanayama M, Wake R, et al. Clostridium butyricum MIYAIRI 588 as Adjunctive Therapy for Treatment-Resistant Major Depressive Disorder: A Prospective Open-Label Trial. *Clinical Neuropharmacology*. 2018;41(5):151-155. doi: 10.1097/wnf.0000000000000299
45. Rudzki L, Ostrowska L, Pawlak D, et al. Probiotic Lactobacillus Plantarum 299v decreases kynurenine concentration and improves cognitive functions in patients with major depression: A double-blind, randomized, placebo controlled study. *Psychoneuroendocrinology*. 2019;100:213-222. doi: 10.1016/j.psyneuen.2018.10.010
46. Akkasheh G, Kashani-Poor Z, Tajabadi-Ebrahimi M, et al. Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. *Nutrition*. 2016; 32(3): 315-320. doi:10.1016/j.nut.2015.09.003
47. Otaka M, Kikuchi-Hayakawa H, Ogura, J, et al. Effect of Lacticaseibacillus paracasei strain shirota on improvement in depressive symptoms, and its association with abundance of actinobacteria in gut microbiota. *Microorganisms.* 2021;9(5):1026. doi: 10.3390/microorganisms9051026
48. Wallace CJK, Milev RV. The Efficacy, Safety, and Tolerability of Probiotics on Depression: Clinical Results From an Open-Label Pilot Study. *Front Psychiatry*. 2021;15;12:618279 doi: 10.3389/fpsyt.2021.618279
49. Chahwan B, Kwan S, Isik A, van Hemert S, Burke C, Roberts L. Gut feelings: A randomised, triple-blind, placebo-controlled trial of probiotics for depressive symptoms. *J Affect Disord*. 2019;253:317-326. doi: 10.1016/j.jad.2019.04.097
50. Reininghaus EZ, Platzer M, Kohlhammer-Dohr A, et al. PROVIT: Supplementary Probiotic Treatment and Vitamin B7 in Depression—A Randomized Controlled Trial. *Nutrients*. 2020;12(11):3422. doi: 10.3390/nu12113422
51. Alli SR, Gorbovskaya I, Liu JCW, Kolla NJ, Brown L, Müller DJ. The Gut Microbiome in Depression and Potential Benefit of Prebiotics, Probiotics and Synbiotics: A Systematic Review of Clinical Trials and Observational Studies. *Int J Mol Sci*. 2022;23(9):4494. doi: 10.3390/ijms23094494