



Modulation of gut microbiota in the therapy of mental disorders – new therapeutic strategies

Modulacja mikrobioty jelitowej w terapii zaburzeń psychicznych: nowe strategie terapeutyczne

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Bystron JM, Dziekiewicz AM. Modulation of Gut Microbiota in the Therapy of Mental Disorders: New Therapeutic Strategies. Med Srod. doi: 10.26444/ms/187949

■ Abstract

Introduction and Objective. In recent years, there has been a rapid increase in the number of people suffering from mental disorders, including depression and anxiety disorders. Data indicate that conventional treatments have not been sufficiently effective, leading to the exploration of alternative methods for treating and preventing these conditions. One of the areas of research is the gut microbiota and its potential role in these disorders. The aim of this study is to summarize the latest evidence linking gut flora to depression and anxiety disorders, and to present ways to alleviate the symptoms of these disorders through proper diet, including the use of prebiotics, probiotics, and synbiotics.

Brief description of the state of knowledge. Research suggests that changes in the gut microbiota may be associated with mental disorders, such as depression and anxiety. Analyses in this area are complex due to the diversity of micro-organisms and the influence of external factors. Treatment methods based on the gut microbiota are becoming a therapeutic alternative for individuals with mental disorders, but further clinical research is required.

Summary. There is a strong correlation between gut dysbiosis, depression and anxiety disorders. These disorders can be effectively alleviated or controlled through modulation of the gut microbiota via proper diet and supplements. Further research is necessary to better understand the relationship between gut dysbiosis and mental disorders and to effectively and safely implement appropriate treatment.

■ Key words

depression, probiotics, anxiety, prebiotics, synbiotics, gut microbiota

■ Streszczenie

Wprowadzenie i cel pracy. W ostatnich latach obserwuje się znaczny wzrost liczby osób cierpiących na zaburzenia psychiczne, w tym depresję i zaburzenia lękowe. Dane pokazują, iż dotychczasowe leczenie nie jest wystarczająco skuteczne, dlatego też zaczęto poszukiwać alternatywnych metod leczenia oraz zapobiegania tymże schorzeniom. Jednym z obszarów badawczych jest mikrobiota jelitowa i jej potencjalna rola w zapobieganiu tym zaburzeniom. Celem tej pracy jest podsumowanie najnowszych dowodów na związek mikroflory jelitowej z depresją i zaburzeniami lękowymi oraz przedstawienie sposobów łagodzenia objawów tych zaburzeń poprzez odpowiednią dietę, w tym stosowanie prebiotyków, probiotyków i synbiotyków.

Opis stanu wiedzy. Badania sugerują, że zmiany w mikrobiocie jelitowej mogą być powiązane z zaburzeniami psychicznymi, takimi jak depresja i zaburzenia lękowe. Analizy tego obszaru są złożone ze względu na różnorodność mikroorganizmów zasiedlających jelita i wpływ czynników zewnętrznych. Metody leczenia oparte na mikrobiocie jelitowej stają się alternatywą terapeutyczną dla osób z zaburzeniami psychicznymi, jednak wymagają dalszych badań.

Podsumowanie. Istnieje silna korelacja między dysbiozą jelitową a depresją oraz zaburzeniami lękowymi. Można skutecznie łagodzić lub kontrolować te zaburzenia poprzez modulację mikrobioty jelitowej za pomocą odpowiedniej diety i suplementów. Konieczne są dalsze badania, aby lepiej zrozumieć związek między dysbiozą jelitową a zaburzeniami psychicznymi oraz skutecznie i bezpiecznie stosować odpowiednie leczenie.

■ Słowa kluczowe

depresja, probiotyki, zaburzenia lękowe, prebiotyki, mikrobiota jelitowa, synbiotyki

INTRODUCTION

According to data presented by the World Health Organization (WHO), 1 in 8 people worldwide suffer from mental disorders. Mental disorders encompass significant disruptions in thinking, emotional regulation, or behaviour. There are many types known. In 2019, 970 million people

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worldwide suffered from mental disorders, with anxiety and depressive disorders being the most common [1]. Mental disorders pose a serious public health problem globally and lead to significant economic losses and medical burdens. In 2020, due to the Covid-19 pandemic, there was a significant increase in the number of people suffering from anxiety and depressive disorders. Preliminary estimates indicate an increase of 26% and 28%, respectively, in just one year [1, 2, 3, 4]. According to research, by 2030, depression may become the most common disease globally, surpassing heart failure [5, 6]. It is also known that the risk of anxiety disorders occurring during a depressive episode is 47–58% higher, and 56% of people with anxiety disorders experience depression [7, 8].

Over the years, numerous studies have demonstrated the association between gut microbiota and mental disorders such as depression and anxiety [4, 9, 10, 11, 12]. It has been found that gut flora can influence the brain and mental health by affecting the vagus nerve and tryptophan metabolism. This happens through microbiological regulation of neuro-immunological signaling, control of neuroendocrine functions, and microbiological production of neuroactive compounds [13, 14]. Gut flora can also produce and regulate neurotransmitters, including dopamine, serotonin, and glutamine, as well as produce short-chain fatty acids and regulate amino acid metabolism pathways, cortisol, and taurine [15, 16].

Although effective methods for treating mental disorders are known, over 75% of people in low- and middle-income countries are not treated [17, 18]. Clinical studies have shown that a significant percentage of patients with severe depressive disorders – Major Depressive Disorder (MDD) – do not respond to currently used first-line antidepressant treatments or do not achieve remission [10, 19]. Only about half of the patients achieve complete remission, and the remission rate decreases with each subsequent treatment [20]. Moreover, many patients with these disorders poorly adhere to currently prescribed antidepressant medications due to their side-effects. This indicates the need for introducing new treatment strategies with fewer side-effects [10].

Knowing the relationship between gut microbiota and mental disorders, new therapeutic methods have been introduced to prevent and treat these disorders, thereby providing an alternative to pharmacotherapy and psychotherapy, which are characterized by limited efficacy and numerous adverse effects [4, 10, 19, 20]. These interventions include probiotics, prebiotics, synbiotics, and faecal microbiota transplantation (FMT).

MATERIALS AND METHOD

Online databases were searched using single keywords and phrases directly related to the topic, utilizing terms such as ‘depression’, ‘anxiety’, ‘gut microbiota’, ‘faecal microbiota transplantation’, ‘probiotics’, ‘prebiotics’, ‘synbiotics’, and ‘gut-brain axis’. Combinations of various key words were additionally created to expand the scope of the search. Although the literature review included works published after 2000, the selection was based on the latest sources available. In total, 97 articles were analyzed, with 48 ultimately selecting that were deemed the most current and relevant to the study. Among those articles, 4 were sourced

from Google Scholar, while the remainder were from the PubMed database. Remarkably, 31 of the cited works were published after 2020.

Depression. Depression is a common mental disorder affecting about 5% of adults. It is characterized by persistent low mood, loss of interest or pleasure over a prolonged period of time [18]. Patients also struggle with anhedonia, changes in appetite and sleep, psychomotor retardation or agitation, feelings of guilt, fatigue, loss of concentration, and suicidal thoughts [10, 21]. It can affect various aspects of daily life, including family life and social interactions. Ferrari et al. in their study demonstrated that MDD contributed to burdens related to suicides and ischemic heart disease, thus emphasizing the importance of including depressive disorders in the public health agenda and implementing cost-effective interventions to reduce their burdens [21]. It occurs 50% more frequently in women, and worldwide over 10% of pregnant and postpartum women experience depression [18, 22].

Numerous studies have shown that gut microbiota dysbiosis is closely associated with the occurrence and development of depression [4]. A study conducted by Chen et al. revealed significant differences in the composition of faecal microbiota in terms of four types of bacteria and the abundance of 16 bacterial families between healthy individuals and patients with MDD [23]. Patients with depression also exhibited a decreased abundance of *Dialister* and *Coprococcus spp*, *Bacteroidetes*, and higher levels of *Prevotella*, *Klebsiella*, *Streptococcus*, and *Clostridium XI* [24, 25]. There is also increasing evidence that women infected with *Helicobacter pylori* are more likely to develop depression [26]. Moreover, premenopausal women with depression were found to have a higher abundance of *Klebsiella aerogenes* bacteria, involved in estradiol breakdown, compared to the control group [27]. Liu et al. discovered that gut microbiota may play a crucial role in the development of depressive behaviours and contribute to changes in protein expression and functions of the gut-brain axis [28]. Several animal studies have also demonstrated significant correlations between gut microbiota dysbiosis and the occurrence of depression. One study showed that macaques exhibiting depressive disorders had a higher abundance of six species of gut bacteria, mainly from the *Paraprevotella* family, but a lower abundance of eight other species of gut bacteria, mainly from the *Streptococcaceae* and *Gemella* families [29]. It was also demonstrated that transferring human depression patient faecal microbiota to germ-free mice was sufficient to reduce sociability and increase susceptibility to learned helplessness, confirming that the microbiota is sufficient to induce depression-like behaviours [30].

Many studies have shown associations between gut microbiota dysbiosis and the occurrence and development of depression. It has been repeatedly observed that the gut microbiota of individuals and animals with depression differ in composition and abundance from that of healthy individuals in a control group. A significant influence on protein expression in tissues related to the gut-brain axis has also been noted. Therefore, gut flora may represent a new significant target in the prevention and treatment of depression [5].

Anxiety disorders. Anxiety disorders are characterized by excessive fear and worry, which can lead to associated behavioural disturbances. They cause significant distress and impair functioning [1]. In 2019, 301 million people suffered from anxiety disorders, including 58 million children and adolescents. Several types of anxiety disorders are identified, including generalized anxiety disorder associated with excessive worry, social phobias causing excessive fear and worry in social situations, and panic disorders associated with panic attacks. Separation anxiety disorder, characterized by excessive fear or anxiety about separation from individuals with whom a person has a deep emotional bond, is also mentioned [1].

Over the years, many studies have demonstrated a close relationship between gut microbiota and anxiety disorders [4]. Kim et al. in their study demonstrated that social exclusion-induced psychological pain is associated with changes in gut microorganisms. They found that in individuals experiencing social exclusion, the abundance of *Prevotella* increased, while the *Firmicutes/Bacteroidetes* ratio and the abundance of *Faecalibacterium spp.* were significantly reduced [31]. In a study conducted by Jiang et al., gut microbiota dysbiosis was identified in patients with Generalized Anxiety Disorder (GAD). It was found that these patients had a higher abundance of *Fusobacteria* and *Bacteroidetes*, decreased levels of *Firmicutes spp.* and microbiota producing Short-Chain Fatty Acids (SCFAs), as well as generally reduced microbial richness and diversity [32]. A study conducted by Malan-Müller et al. also analyzed microbial features in faeces related to mental health post-Covid-19 pandemic. The results indicated that individuals suffering from anxiety disorders had lower microbial diversity, as confirmed by the Simpson index. In individuals with comorbid Post-Traumatic Stress Disorder (PTSD), depression, and anxiety symptoms, a decrease in the presence of *Fusicatenibacter saccharivorans* was observed.

Moreover, individuals with depressive symptoms showed an increase in the number of bacteria from the *Proteobacteria phylum* and a decrease in the number of bacteria from the *Synergistetes phylum*. A positive correlation was also found between the abundance of *Anaerostipes* and childhood traumatic events, as well as associations between higher levels of *Turicibacter sanguinis* and lower levels of *Lentisphaerae* with the occurrence of life-threatening injuries [33]. Yuan et al. found that compared to patients with Ulcerative Colitis (UC) without depression/anxiety, patients with UC and depression/anxiety exhibited lower microbial richness and diversity in faeces. They had a higher number of *Lactobacillales*, *Streptococcus*, *Sellimonas*, and *Enterococcus bacteria*, but fewer *Lachnospira* and *Prevotella* [8]. There was a general decrease in immunoglobulin proteins as well as an increase in the concentration of most serum metabolites, while the concentration of several metabolites, including 2'-deoxy-D-ribose and L-pipecolic acid, decreased [34].

There are many studies confirming a close relationship between gut microbiota and anxiety disorders. A thorough analysis of microbiome components in different anxiety states is necessary to effectively develop necessary therapeutic and preventive goals, thereby providing an alternative to currently used treatment methods.

MODULATION OF GUT MICROBIOTA BY THERAPEUTIC MICROBIAL INTERVENTIONS

Probiotics. In exploring therapeutic options for anxiety and depression, probiotics emerge as a potential avenue worth considering. Studies by Kim et al. and Nikolova et al. suggest promising results regarding the impact of probiotic supplementation on mental health [35, 36]. Kim et al. found that probiotic supplementation contributed to improvements in cognitive and cerebral functioning in older adults, potentially mediated by interactions between gut microbiota and the central nervous system [36]. Similarly, Nikolova et al. concluded that adjunctive treatment with a multi-strain probiotic was acceptable and tolerated by adults with MDD [35]. However, Chahwan et al.'s study highlights the need for cautious interpretation, indicating that while some probiotic mixtures may influence thinking and cognition, they may not necessarily lead to significant reductions in depressive symptoms [37]. Despite mixed findings, probiotics remain a compelling area of research within the context of gut microbiota and mental health, warranting further investigation into their potential therapeutic benefits for anxiety and depression.

Faecal microbiota transplantation (FMT). Faecal Microbiota Transplantation (FMT) emerges as a promising avenue for modulating the microbiota and treating conditions such as depression, where conventional therapies often fall short. Unlike probiotics, which offer a limited selection of bacterial strains, FMT presents a comprehensive approach by incorporating the diverse bacterial ecosystem of the human gut. Research suggests that FMT-induced alterations in gut microbiota composition can influence psychiatric behaviours, as evidenced by studies demonstrating depression-like behaviours in rodents following FMT from depressed humans [38, 39, 40]. Additionally, case studies and open-label trials suggest promising outcomes in treating depressive symptoms and bipolar disorder with FMT [41, 42]. Furthermore, FMT has shown concurrent improvements in mental health symptoms in disorders such as Irritable Bowel Syndrome (IBS), which commonly co-occurs with depression. Pioneering trials like The Moving Moods Pilot Study employ a randomized, double-blinded, placebo-controlled design, shedding light on FMT's feasibility and safety. The study found that enema-delivered FMT is well-tolerated and potentially effective as an adjunctive treatment for MDD, observing improvements in gastrointestinal symptoms and quality of life [38]. Moreover, FMT emerges as a rapid and promising intervention strategy for chronic diseases linked with dysbiosis, reshaping the patient's gut microbiota by administering faecal flora from healthy donors. In preclinical studies, FMT demonstrates efficacy in alleviating depressive-like behaviour, with microbiota transplantation from healthy donors relieving alcohol-induced depressive-like behaviour in mice and improving stress-induced depression phenotypes in rats by addressing neuroinflammation, gut microbiota imbalance, and intestinal barrier damage. The vagus nerve likely serves as a significant signaling route in the gut-brain axis, mediating FMT's protective effects on depression. Notably, FMT treatment in patients with Diarrhea-predominant Irritable Bowel Syndrome (IBS-D) gradually improves depression symptoms, regardless of gastrointestinal symptom remission, as supported by Randomized Controlled

Trials (RCTs). Moreover, RCTs assessing the efficacy of oral frozen FMT-capsules as add-on therapy in MDD patients have reported significant improvements in depressive symptoms. Similar to autism, FMT therapy for depression not only improves gastrointestinal symptoms but also rebalances the gut ecosystem [38, 41]. Despite reports of adverse effects and complications, including those associated with standard FMT procedures, alternative pills derived from human faeces are gaining attention for their less invasive and more standardized approach, further advancing FMT's potential in scientific research and clinical applications.

Synbiotics and prebiotics. Synbiotic and prebiotic interventions offer promising avenues for addressing both clinical and psychological aspects of anxiety and depression. Studies conducted by Hadi et al. and Haghghat et al. demonstrated significant improvements in various health markers, including body weight, lipid profile, stress, anxiety, and depression, among overweight or obese individuals and hemodialysis patients with depressive symptoms, respectively [43, 44]. Hadi et al.'s study, involving overweight or obese adults, revealed notable enhancements in total cholesterol, triglycerides, LDL-C, and mental health parameters following synbiotic supplementation. Although limitations, such as the inability to measure faecal bacterial profiles were acknowledged, the study highlighted the potential benefits of synbiotic consumption in this population [43]. Similarly, Haghghat et al.'s research emphasized the significant increase in serum Brain-Derived Neurotrophic Factor (BDNF) levels and reduction in Hospital Anxiety and Depression Scale (HADS) scores among haemodialysis patients with depressive symptoms receiving synbiotic supplementation [44]. These findings suggest that synbiotic supplements may influence depression through modulation of BDNF levels, particularly in patients with comorbid depression. However, Alli et al.'s review underscores the need for further rigorous double-blind randomized controlled trials to elucidate the precise effects of synbiotic supplementation on depression symptoms, taking into consideration such factors as symptom severity, age, diet, and medication use [45]. Despite promising results,

additional research is warranted to establish the optimal dosing regimens, and to better understand the interplay between genetic and microbiome variations in treatment response.

Regarding prebiotics, substances that selectively stimulate the growth and activity of beneficial bacteria in the gut, they offer promising prospects in managing anxiety, depression, and related inflammatory conditions. Mysonhimer et al.'s investigation on prebiotic effects in healthy adults revealed increased levels of *Bifidobacterium* in the gut without significant impacts on stress, inflammation, or mental health symptoms, highlighting the complex interplay between prebiotic consumption and psychological well-being [46]. Conversely, Moludi et al.'s study on patients with coronary artery disease demonstrated the synergistic benefits of combining probiotic *Lactobacillus rhamnosus* GG with prebiotic Inulin in reducing depression, anxiety, and inflammation more effectively than when administered separately [47]. Although limitations such as short intervention periods and lack of gut microbiota analysis were noted, the study underscores the potential of probiotic-prebiotic synergy in ameliorating mental health and inflammatory markers in cardiovascular patients. Similarly, Othman et al.'s research on obese individuals revealed favourable outcomes in weight loss, improved metabolic parameters, and reduced psychiatric disorders when prebiotics and probiotics were combined with lifestyle changes [48]. Despite limitations including small sample sizes and short intervention durations, these findings advocate for the incorporation of prebiotics in therapeutic strategies for anxiety, depression, and associated inflammatory conditions, underscoring the importance of modulating the gut microbiota for holistic well-being.

After discussing various therapeutic interventions targeting gut microbiota in the management of anxiety and depression, it is beneficial to summarize the key findings and its potential impact in a structured manner. The following Table provides an overview of different therapeutic approaches, including probiotics, FMT, synbiotics, and prebiotics, along with their significant findings and potential impact in relation to anxiety and depression management.

Table 1. Therapeutic interventions targeting gut microbiota in the management of anxiety and depression – key findings and potential impact [31, 35, 37, 43, 44, 46, 47]

Therapeutic Microbial Interventions	Key Findings	Potential impact
Probiotics	<ul style="list-style-type: none"> Improvement in cognitive and cerebral functioning in older adults. Acceptability and tolerability in adults with MDD. Influence on thinking and cognition, but not significant reductions in depressive symptoms. 	<ul style="list-style-type: none"> Enhances cognitive and mental health in older adult. Provides adjunctive treatment option for MDD. Partial influence on cognition, but may not significantly reduce depressive symptoms.
Fecal Microbiota Transplantation	<ul style="list-style-type: none"> Promising outcomes in treating depressive symptoms and bipolar disorder. Improvement in mental health symptoms in IBS. Significant improvements in stress-induced depression phenotypes (Preclinical studies). 	<ul style="list-style-type: none"> Novel therapeutic option for depression and related disorders. Potential for concurrent improvements in mental health and gastrointestinal symptoms. Rapid and promising intervention for dysbiosis-related chronic diseases.
Synbiotics	<ul style="list-style-type: none"> Improvement in various health markers in overweight or obese individuals. Increased serum BDNF levels and reduced depression and anxiety symptoms in hemodialysis patients. 	<ul style="list-style-type: none"> Potential for improving metabolic and mental health parameters in overweight or obese individuals. Influence on depression symptoms through modulation of BDNF levels in patients with comorbid depression.
Prebiotics	<ul style="list-style-type: none"> Increased levels of <i>Bifidobacterium</i> without significant impacts on stress or inflammation. Synergistic benefits in reducing depression, anxiety, and inflammation when combined with probiotics in coronary artery disease patients. 	<ul style="list-style-type: none"> Highlights the complexity of prebiotic consumption and its impact on psychological well-being. Demonstrates potential for synergistic effects with probiotics in managing depression, anxiety, and inflammation in cardiovascular patients.

CONCLUSIONS

The interplay between gut microbiota and mental health disorders, particularly depression and anxiety, presents a significant avenue for research and therapeutic interventions. Understanding the intricate relationship between the gut-brain axis and the bi-directional communication pathways involved, opens doors to novel treatment modalities that offer potential benefits beyond traditional pharmacotherapy and psychotherapy. The emergence of therapeutic microbial interventions, including probiotics, FMT, synbiotics, and prebiotics, hold promise in modulating gut microbiota composition and addressing mental health challenges.

- Probiotic supplementation shows potential in improving cognitive function and alleviating symptoms of depression, although further research is needed to fully elucidate its efficacy.
- FMT, with its comprehensive approach to restoring gut microbial diversity, offers promising results in treating depression and associated disorders, highlighting the importance of microbiota transplantation in reshaping the gut ecosystem and alleviating depressive-like behaviours.
- Synbiotic supplementation, combining probiotics and prebiotics, demonstrates beneficial effects on mental health markers, offering a holistic approach to managing anxiety and depression.
- Prebiotics, which selectively stimulate beneficial bacteria in the gut, show promise in reducing depression and anxiety symptoms, especially when combined with probiotics, suggesting the importance of synergistic approaches in modulating the gut microbiota for mental health benefits.

Overall, the modulation of gut microbiota through therapeutic microbial interventions presents a promising frontier in mental health care, offering alternative avenues for prevention and treatment that warrant further exploration and clinical validation. As research in this field continues to evolve, it holds the potential to revolutionize our approach to managing mental health disorders, providing personalized and effective interventions that address the underlying biological mechanisms involved in depression and anxiety.

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