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The role of probiotics in the treatment of depressive disorders. A critical review

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ABSTRACT

Depressive disorders are a widespread problem in modern medicine. According to current data from the World Health Organisation, an estimated 280 million people worldwide suffer from depression. In recent years, there have been reports of a correlation between the composition of the gut microbiota and the development of depressive disorders and attempts to modify it through the use of psychobiotics.

The literature from the PubMed database published between 2018-2023 has been explored. 596 articles were selected based on the keywords "*probiotics*" and "*depression*". Six randomized clinical trials were finally included in the analysis.

As defined elsewhere, psychobiotics are probiotic bacteria which supplemented in adequate amounts, interact with the gut-brain axis and show beneficial effects on patients' mental health. Results from recent RCTs suggest that daily probiotic supplementation significantly reduces the severity of depression compared to placebo ($p < 0.05$). Additionally, this effect may be enhanced by the combined use of a probiotic with a prebiotic. Furthermore, some researchers indicate that probiotics may lead to significant improvements in cognitive function in patients suffering from depressive disorders.

In conclusion, intestinal dysbiosis may be an important factor leading to the development of mental illness. Results of recent studies suggest that specific strains of probiotic bacteria may offer therapeutic benefits in the treatment of the aforementioned disorders. However, further clinical studies are needed to objectively confirm the relationship between gut microbiota composition and the development of depression.

Key words: probiotics; gut microbiota; depression

INTRODUCTION

Depression is a widespread problem in the modern world and one of the leading causes of disability and incapacity. Its prevalence ranges from 2.6% to 5.9%. The most common age of diagnosis is between 20 and 40 years. However, almost 40% of people experience their first episode before the age of 20. Female gender is a significant risk factor for depressive disorders. In women depression is twice more common in comparison to men. The lifetime risk of developing a depressive disorder is close to 15-18%, meaning that the illness affects almost one in five people at some point in their lives. In primary care settings, an average of one in ten patients has depressive symptoms. [1] According to the World Health Organization (WHO), 280 million people worldwide suffer from depression (approximately 3.8% of the population). It affects 5.0% of adults and 5.7% of people aged 60 and over. The diagnosis is increasingly common in adolescents and children. [2,3] In Poland, an estimated 1.2 million people suffer from depression. The National Health Fund's 2023 report states that reimbursed antidepressants (used for depression, but also for other mental disorders) were purchased in 2021. 1.5 million people and this was 59% more than in 2013. [4]

Many therapeutic options are currently available, including pharmacological interventions. However, due to treatment-resistant depression and the delayed onset of action of first-line antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), the needs of many patients are unmet. This prompts the search for new pharmacotherapy options. [5]

In recent years, increased attention has been focused on the concept of the gut-brain axis, which represents a bidirectional communication between the gut microbiota and the Central Nervous System (CNS). [6] It is formed by an endocrine pathway via the HPA axis, a metabolic pathway via short-chain fatty acids (SCFAs), an immune pathway via cytokines and immunocompetent compounds, as well as the vagus nerve and the enteric nervous system. [7]

The microbiota has an important impact on people's health. The gut contains 10¹⁴ microorganisms, which is 100 times the number of cells in the human body. [8] Some studies suggest that the gut microbiota has a significant role in the neurodevelopment and etiopathogenesis of some neuropsychiatric disorders. [9] There are reports that microbial colonization in infants coincides with crucial periods of neurodevelopment. Furthermore, impaired gut colonization in early life may be associated with central nervous system dysfunction and potentially lead to adverse mental health outcomes later in life. [10]

Following this line of thought, there are increasing reports of a correlation between the composition of the gut microbiota and the development of depressive disorders. There are attempts to modify it through the use of psychobiotics.

MATERIAL AND METHODS

The aim of this work is to evaluate the potential therapeutic benefits of specific probiotic bacterial strains in the treatment of depressive disorders. The literature from the PubMed database published between 2018-2023 has been explored. Only articles in English were eligible for further analysis. Based on the keywords "*probiotics*" and "*depression*" 596 articles were selected. Finally, 6 randomized clinical trials, consistent with the topic of the paper, were included in the analysis.

RESULTS

TABLE.1 CHARACTERISTICS OF THE STUDIES INCLUDED

No.	Author	Year	Study design	Test group	Control group	Duration of the study	Intervention	Results
1	Peijun Tian et al.	2022	Randomized, double-blind controlled trial	n=20	n=25	Daily supplementation for 4 weeks	Bifidobacterium breve CCFM1025	Significant reduction in depression severity (p<0.05)
2	Asma Kazemi et al.	2019	Randomized, double-blind controlled trial	n=28 (probiotic) n=27 (prebiotic)	n=26	Daily supplementation for 8 weeks	Lactobacillus helveticus R0052, Bifidobacterium longum R0175	Significant reduction in depression severity in the probiotic supplement group (p<0.05) compared to placebo
3	Neda Haghghat et al.	2021	Randomized, double-blind, controlled trial	n=25 (probiotic) n=25 (synbiotic)	n=25	Daily supplementation for 12 weeks	Lactobacillus acidophilus, Bifidobacterium bifidum, Bifidobacterium longum	Significant reduction in depression severity in the synbiotic supplement group compared to placebo and

								probiotic (p<0.05)
4	Bahia Chahwan et al.	2019	Randomized, triple-blind controlled trial	n=34	n=37	Daily supplementation for 8 weeks	Ecologic® Barrier (i.a. Bifidobacterium bifidum W23, Bifidobacterium lactis W51, Lactobacillus brevis W63)	No significant reduction in depression severity compared to placebo (p>0.05)

A placebo-controlled, double-blind Randomized Controlled Trial by Peijun Tian et al. 2022 (Table 1) assessed the psychotropic potential of Bifidobacterium breve CCFM1025 in the treatment of major depressive disorder (MDD). Forty-five patients above 18 years of age diagnosed with MDD without antidepressant medication restrictions were randomly allocated to placebo (n=25) and CCFM1025 (n=20) groups. CCFM1025 (with a total viable bacteria of 10¹⁰ CFU) was administered to study participants daily for four weeks. The placebo group received maltodextrin. Changes from baseline were assessed using the Hamilton Depression Rating Scale (HDRS-24), the Montgomery-Asberg Depression Rating Scale (MADRS), the Brief Psychiatric Rating Scale (BPRS) and the Gastrointestinal Symptom Rating Scale (GSRS). The results of the study indicate a significant reduction in depression severity (p<0,05) according to the HDRS-24 and MADRS scales compared to placebo. In addition, a reduction in the severity of gastrointestinal symptoms (p<0.05) and a reduction in serum serotonin turnover (p<0.05) were demonstrated compared to the placebo. This may be explained by changes in the gut microbiome and tryptophan metabolism in the gut under the influence of probiotic treatment. However, the study did not find a statistically significant difference in changes in serum cortisol and inflammatory cytokine levels due to probiotic administration (p>0.05). [11]

In 2019, Asma Kazemi et al. conducted a placebo-controlled, double-blind Randomized Controlled Trial (Table 1) to compare the effect of probiotic and prebiotic supplementation on Beck Depression Inventory (BDI) scores. The study included 81 participants. Inclusion criteria included patients with mild to moderate depression aged 18-50 years who had been taking antidepressants (sertraline, fluoxetine, citalopram or amitriptyline) for three months or longer before the start of the trial. Participants were randomly allocated to placebo (n=26), probiotic (*Lactobacillus helveticus* and *Bifidobacterium longum*) (n=28) and prebiotic (galactooligosaccharide) (n=27) groups. Daily supplementation lasted 8 weeks. The results of the study show a significant reduction in depression severity according to the BDI scale in the probiotic supplement group ($p<0.05$) compared to placebo. The decrease in symptom intensity in the prebiotic supplement group was not statistically significant compared to placebo and probiotics ($p>0.05$). Furthermore, there was a reduction in the ratio of kynurenine to tryptophan in the probiotic group ($p<0.05$) compared to placebo. Tryptophan is a precursor of serotonin, so the decrease in this ratio may have been related to enhanced serotonin production through tryptophan pathway metabolism. [12]

A placebo-controlled, double-blind Randomized Controlled Trial by Neda Haghghat et al. 2021 (Table 1) evaluated the effect of probiotic and synbiotic supplementation on reducing symptoms of depression and anxiety. Seventy-five hemodialysis patients aged 30-65 years were included in the study. Participants were randomly assigned to receive a synbiotic (*Lactobacillus acidophilus* T16, *Bifidobacterium bifidum* BIA-6, *Bifidobacterium lactis* BIA-7 and *Bifidobacterium longum* BIA-8 at 7×10^7 CFU/each with a prebiotic) or a probiotic (as above) or placebo (maltodextrin) for 12 weeks. Each group consisted of 25 patients. The results of the study show a significant reduction in depression severity according to the Hospital Depression and Anxiety Scale (HADS) in the synbiotic supplement group compared to placebo and probiotics ($p<0.05$). In addition, the trial reported a significant increase in serum BDNF levels in the synbiotic group compared to placebo and probiotics ($p<0.05$). BDNF is a neuroprotein that promotes neuronal survival and differentiation and has been implicated as a regulatory protein in the pathophysiology of depression and anxiety. In general, synbiotic supplementation resulted in greater improvements in depressive symptoms and BDNF levels compared to probiotic supplementation, especially in the subgroup of patients with depressive symptoms. The higher efficacy of synbiotic supplementation may be related to the synergistic effects of pre- and probiotic therapy on the stability of the gut microbiota. [13, 14]

However, the results of the study are not entirely consistent. Another placebo-controlled, triple-blinded Randomized Controlled Trial, conducted by Bahia Chahwan et al. 2019 (Table 1), involved 71 patients over 18 years of age with depressive symptoms. Participants were not allowed to take any medication, including antidepressants. They were randomly assigned to the probiotic (n=34) or placebo (n=37) group. The study lasted 8 weeks. The probiotic group received Ecologic®Barrier (2.5 x 10⁹ CFU/g), containing Bifidobacterium bifidum W23, Bifidobacterium lactis W51, Lactobacillus brevis W63, among others. The results of the trial show that there was no significant reduction in the severity of depression according to the BDI and DASS-21 (the Depression Anxiety Stress Scale – 21) scale compared to placebo (p>0.05). No major changes in the microbiota were also observed. The study leads to the conclusion that probiotics alone are not an effective treatment option for depressive disorders. [15]

TABLE 2. CHARACTERISTICS OF THE STUDIES INCLUDED

No.	Author	Year	Study design	Test group	Control group	Duration of the study	Intervention	Results
1	Leszek Rudzki et al.	2019	Randomized, double-blind, controlled trial	n=30	n=30	Daily supplementation for 8 weeks	Lactobacillus Plantarum 299v	Improvement in cognitive function compared to placebo (p<0.05)
2	Else Schneider et al.	2023	Randomized, double-blind, controlled trial	n=21	n=26	Daily supplementation for 4 weeks	Vivomixx (i.a. Streptococcus thermophilu, Bifidobacterium breve, B. infantis, L. acidophilus)	Improvement in cognitive function compared to placebo (p<0.05)

In addition to this, some researchers indicate that probiotics can lead to significant improvements in cognitive function in patients suffering from depressive disorders. The aim of the 2019 Randomized Controlled Trial by Leszek Rudzki et al. (Table 2) was to evaluate the psychobiotic and immunomodulatory effects of Lactobacillus Plantarum (LP299v) in

patients with MDD on selective serotonin reuptake inhibitors (SSRIs). 60 participants were randomly assigned to a probiotic supplement group (n=30) or a placebo group (n=30) for 8 weeks. The results suggest that enhancing SSRI relevance with *Lactobacillus Plantarum* 299v bacteria improved cognitive performance in patients with MDD. This may be related to the decrease in serum kynurenine levels caused by the probiotics. [16]

The potential of probiotics in the treatment of cognitive symptoms in depression was also evaluated in a Randomized Controlled Trial by Else Schneider et al. published in 2023. Participants were randomly assigned to a probiotic supplement group (n=21) or a placebo group (n=26) for 4 weeks. All were over 18 years old and on standard treatment for depression. The probiotic supplement administered was Vivomixx, which includes *Streptococcus thermophilus*, *Bifidobacterium breve*, *B. infantis*, *L. acidophilus*, among others. Patients received a daily dose of 900 billion CFU. The results of the study suggest that additional probiotic supplementation improves verbal episodic memory and affects the neuronal mechanisms underlying cognitive impairment in MDD, which may be related to the effects of psychobiotics on hippocampal function. [17]

DISCUSSION

In 2013, Dinan and colleagues defined the term 'psychobiotics' as probiotic bacteria that, when supplemented in adequate amounts, affect the gut-brain axis and show beneficial effects on patients' mental health. [18] Sarkar et al. suggested extending this definition to include any other substances that may cause positive changes in the microbiome. They suggested that prebiotics, which promote the growth of bacteria with psychobiotic potential, should also be included in the definition. [19] Psychobiotics differ from their conventional probiotic counterparts by producing and stimulating specific molecules that manipulate gut-brain signals. All psychobiotics are probiotics, but not all probiotics are psychobiotics. [20] In the available literature, the strains with the best-documented psychobiotic effects are *Bifidobacterium* and *Lactobacillus*. Their potential mechanisms of action include modification of hypothalamic-pituitary-adrenal (HPA) axis activity and glucocorticosteroid release, restoration and maintenance of the proper intestinal barrier, effects on cannabinoid receptor function in the spinal cord, modulation of anti-inflammatory cytokine balance, beneficial effects on neurotransmitter synthesis: serotonin (5-HT), γ -aminobutyric acid (GABA) and brain-derived neurotrophic factor (BDNF). Some strains of *Lactobacillus* spp. and *Bifidobacterium* spp. such as *Lactobacillus brevis*, *Bifidobacterium dentium* and *Lactobacillus plantarum* produce GABA and serotonin. In addition, *Lactobacillus* strains such

as *L. plantarum* and *Lactobacillus odontolyticus* produce acetylcholine. Recently, spore-forming bacteria from the gut microbiota have been found to induce serotonin biosynthesis from gut enterochromaffin cells. [8, 21, 22]

The results of recent studies suggest that the use of psychobiotics as a dietary supplement may prove to be an important treatment option for depression. These products have a low likelihood of adverse events and have been found to be safe for long-term administration. [23] However, there are several concerns associated with these supplements. Many properties of psychobiotics are strain-specific. Thus, efficacy findings associated with specific formulations should not be generalized to other probiotic preparation. It cannot be assumed that findings for one psychobiotic will translate into clinical utility for another strain. In addition, some probiotics may require caution when used in patients with weakened immune systems, leaky gut or critical illnesses. Supplementation with probiotic preparations may be associated with the side effect of partial reversal of some of the benefits if their administration is abruptly discontinued. This suggests that continuous dosing may be required in some cases. [20]

In some studies, no significant changes in the gut microbiota were observed before and after the intervention, either in the probiotic or placebo group. However, there are reports that probiotics can modulate gene expression of the gut microbiota in the absence of compositional changes, with potential anti-inflammatory and antidepressant effects. Beyond this, modulation of the microbiota may require more detailed testing to distinguish subtle changes. [24,15]

Current knowledge of brain-gut-microbiota interactions in relation to psychiatric disorders is mostly based on preclinical studies. Preliminary trials in psychiatric populations support the view of gut dysbiosis in some disorders. The problem is that these studies are small-scale and fraught with potential confounding variables, such as patients' age and genotype, diet or comorbidities. It should also be taken into account that the reported changes in mental status may be more a reflection of natural or spontaneous recovery over time than a result of probiotic administration. There is a need for more human clinical trials. [25, 15]

CONCLUSIONS

In conclusion, intestinal dysbiosis may be an important factor leading to the development of mental illness. Results from recent studies suggest that specific strains of probiotic bacteria may offer therapeutic benefits in the treatment of depressive disorders. However, due to inconsistent results, further clinical research is needed to objectively confirm the relationship

between gut microbiota composition and the development of depression. Future trials should not only focus on evaluating the therapeutic efficacy of probiotic preparations. It is also important to determine the potential beneficial effects of probiotic therapy depending on the severity of depression and to assess the usefulness of daily supplementation in preventing the development of depression in predisposed individuals.

Author Contributions

Conceptualization: Aneta Głaz, Kinga Knop-Chodyła, Anna Kochanowska-Mazurek; Methodology: Aneta Głaz, Damian Wach; Validation: Kinga Knop-Chodyła, Zuzanna Piasecka, Ewelina Wesolek; Formal Analysis: Aneta Głaz, Beata Kasztelan-Szczerbińska, Barbara Skrzydło-Radomańska; Investigation: Aneta Głaz, Damian Wach, Anna Kochanowska-Mazurek; Resources: Aneta Głaz, Kinga Knop-Chodyła, Zuzanna Piasecka; Data Curation: Aneta Głaz, Anna Kochanowska-Mazurek, Beata Kasztelan-Szczerbińska; Writing – Original Draft Preparation: Aneta Głaz, Damian Wach, Kinga Knop-Chodyła, Ewelina Wesolek; Writing - Review & Editing: Beata Kasztelan-Szczerbińska, Barbara Skrzydło-Radomańska; Visualization: Aneta Głaz; Supervision: Beata Kasztelan-Szczerbińska, Barbara Skrzydło-Radomańska; Project Administration: Damian Wach, Zuzanna Piasecka.

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Conflicts of Interest

The authors declare no conflict of interest.

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