

# The use of probiotics in the treatment of selected psychiatric disorders

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## Abstract

**Aim:** Probiotics are live microorganisms that are part of the human microbiota. The intestines are the habitat for approximately  $10^{13}$ - $10^{14}$  microorganisms, mainly Firmicutes and Bacteroidetes. The gut microbiota is an individual characteristic for each person and can change due to many factors, including: age, diet, and health status. The gut microbiota plays a key role in the proper functioning of the brain-gut axis, thus contributing to human health and mental well-being. The aim of this study was to present the effect of probiotic use in the course of selected psychiatric disorders.

**Material and methods:** The literature review was performed using information from PubMed/Medline, ScienceDirect, and Polish Psychiatry databases that were published before 2022.

**Results and discussion:** A factor associated with disorders such as depression, autism, Alzheimer's disease, and mental anorexia is the generalized inflammation taking place in the patient's body. Research indicates that the inflammatory response may be caused by an imbalance in the intestinal barrier and disruption of its continuity, which may result in translocation of bacteria into the blood and activation of the immune system. The use of probiotics may play a significant role in maintaining the bacterial balance in the gastrointestinal tract and the proper functioning of the gut-brain axis, which provides a link between gut function and the emotional and cognitive centers of the brain.

**Conclusions:** Probiotics may improve mental health and cognitive function, but more clinical studies are needed on the clinical significance of the effects and how they compare to current therapies.

**gut microbiota, depression, anorexia nervosa, autism, Alzheimer's disease**

## INTRODUCTION

The human gut microbiota represents the largest microbial population of the human microbiota [1]. The gut microbiota consists of thousands of microorganisms, including bacteria, viruses, and some eukaryotes, which colonize the gastrointestinal tract immediately after birth [2]. Moreover, the gut microbiota is an individual char-

acteristic for each person and changes due to many factors, including age, diet, lifestyle, and health status [3, 4]. Diet appears to be one of the most important factors influencing the composition and development of the human microbiota. With the increase in people's nutritional awareness, there is an increasing desire not only to satisfy hunger, but also to consume products that have a health effect or perform other physiological and nutritional functions, preventing diseases such as atherosclerosis, cancer, hypertension, tooth decay. These products may include probi-

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otic foods [2, 3]. The intestinal microbiota is responsible for many important functions in the human body: providing protection against pathogens by colonizing mucosal surfaces and producing various antimicrobial substances, as well as strengthening the immune system [4]. It also plays an important role in: digestion and metabolism [5], controlling epithelial cell proliferation and differentiation [6], or modifying insulin sensitivity [7, 8]. The gut microbiota affects the communication between the gut and the brain and thus influences the mental and neurological functions of the host [9], thus the gut microbiota plays an important role in maintaining normal physiology and health.

The aim of this study was to evaluate the effectiveness of probiotics in the treatment of selected neurodevelopmental, emotional and neurodegenerative disorders. The literature review was performed using information from PubMed/Medline, ScienceDirect and Psychiatry Polska databases, which were published before 2022. The databases were searched using the following keywords: „probiotic”, „mental disorders”, „microbiota”, „gut – brain axis”, „psychiatric disorders” and the term „dysbiosis”.

## PROBIOTIC

Probiotics are live microorganisms that are part of the human microbiota, when consumed in adequate amounts they have a positive effect on the health of the host. A strain exhibiting clinically documented beneficial health effects is considered a probiotic strain, but this refers to a single strain tested, not to a species, genus, or total lactobacilli. Probiotic strains include lactic acid bacteria (*Lactobacillus* spp., *Streptococcus* spp.), yeast (*Saccharomyces* spp.), and mold cultures (*Aspergillus* spp.) [10]. The beneficial changes that occur in the host under the influence of probiotics are an increase in the number of beneficial intestinal microbiota, and in diseased individuals, a decrease in the number of harmful microbiota and restoration of balance between strains [10].

A psychobiotic is a probiotic preparation that shows health benefits in healthy patients and those being treated for emotional and mental disorders through interaction with commensal gut bacteria. Microbial imbalances in the gut have

been shown to play a role in the pathogenesis and influence the clinical course of neurodevelopmental (autism) and emotional disorders (depression, schizophrenia) and neurodegenerative conditions (Parkinson’s and Alzheimer’s disease) [11, 12].

## Description of the state of the art

Impact of probiotic use in the treatment of selected psychiatric disorders

### Depression

Depression is a common mental disorder that can be long-lasting or recurrent, significantly impairing the ability to function in everyday life. Depression belongs to a group of mental disorders most commonly manifested by: lowered mood, lack of energy, sadness, insomnia, and lack of enthusiasm. Because of the prevalence and impact of depressive symptoms on daily functioning, they are a growing public health concern. Nearly 20% of the population suffers from depression at some point in their lives. Currently, depression affects 350 million people, and the population with depression is gradually multiplying [13, 14, 15].

Low-grade inflammation in the body plays an important role in the pathophysiology of depression [16, 17, 18]. In addition, a general dysregulation of neurotransmitters such as serotonin (5-HT), dopamine and norepinephrine has also been linked to the development of depression. The metabolism of the amino acid tryptophan (Trp) plays a major role in all these processes. This amino acid is obtained exclusively from the diet and plays an essential role in a number of physiological reactions. Its metabolism to 5-HT and kynurenine (Kyn) plays a key role in depression [19].

Studies in mice have shown that disrupting the microbiota caused the animals to exhibit behaviors that mimic human depression, leading to the conclusion that dietary treatment can be used as a monotherapy or adjunctive therapy for mood disorders. It was shown that a strain of *Bifidobacterium infantis* used in rats showed effects similar to citalopram (a chemical compound belonging to the serotonin reuptake in-

hibitor group), an agent used to treat symptoms of depression. Probiotic therapy with the *Bifidobacterium infantis* strain [20, 21] led to normalization of the immune response and reduction of depressive symptoms. A weakening of pro-inflammatory immune responses and an increase in tryptophan, an amino acid involved in serotonin production, were also observed, suggesting that this probiotic may have antidepressant properties [20, 21]. It was also shown that a combination of *Lactobacillus helveticus* and *Bifidobacterium longum* reduced the severity of depressive symptoms in the rat [22] (Table 1).

A multi-species probiotic containing *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52,

*Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24 and *Lactococcus lactis* W19 and W58 showed positive anti-stress effects in humans [23]. It was also shown that the combination of *Lactobacillus helveticus* and *Bifidobacterium longum* reduced the severity of depressive symptoms in humans [22] (Table 2).

An analysis of studies showed that the incidence of depression was significantly reduced in the group taking probiotics compared to the group not taking probiotics. This suggests that the probiotic intervention may have an antidepressant effect.

**Table 1.** Probiotics in rodent models of depression

Strain names	Dosage	Duration of intervention	Surveys used to evaluate primary outcome	Outcome	Refs
<i>Bifidobacterium infantis</i> 35624	1 x 10 <sup>10</sup> live bacterial cells	14 days	Forced swim test (FST); Animal sacrifice, blood collection and tissue dissection; Whole blood culture; Cytokine analysis: flow cytometry; Plasma tryptophan pathway analysis: HPLC; Brain monoamine analysis: HPLC; AVP, CRF mRNA analysis: Real Time PCR; Plasma corticosterone analysis: enzyme immunoassays; Statistical analyses	Reduction of pro-inflammatory immune responses. Increased concentrations of the serotonin precursor, tryptophan.	[20]
<i>Bifidobacterium infantis</i> 35624	1 x 10 <sup>10</sup> live bacterial cells	From postnatal day 50 to the day of sacrifice	FST; Animal sacrifice and tissue dissection; Corticosterone enzyme immunoassay (EIA); Whole blood culture; flow cytometry; Brain monoamine analysis: HPLC; Plasma tryptophan pathway analysis: HPLC; CRF, AVP mRNA isolation, c-DNA reverse transcription and real time-PCR; Statistical analyses	Normalization of the immune response, reversal of behavioral deficits, and restoration of basal noradrenaline concentrations in the brainstem	[21]
<i>L. helveticus</i> R0052 + <i>B. longum</i> R0175	1x 10 <sup>9</sup> CFU	14 days	Conditioned defensive burying	Lower levels of stress in rats treated with probiotic and diazepam, compared to the control group in the shock test	[22]

**Table 2.** Probiotics in human models of depression

Strain names	Dosage	Duration of intervention	Surveys used to evaluate primary outcome	Outcome	Refs
<i>Bifidobacterium bifidum</i> W23, <i>Bifidobacterium lactis</i> W52, <i>Lactobacillus acidophilus</i> W37, <i>Lactobacillus brevis</i> W63, <i>L. casei</i> W56, <i>Lactobacillus salivarius</i> W24, and <i>Lactococcus lactis</i> (W19 and W58)	2.5 x 10 <sup>9</sup> CFU/g (dosage 2g)	28 days	Questionnaires: The LEIDS-r; The Beck Depression Inventory II; The Beck Anxiety Inventory; Statistical analyses	The intake of multispecies probiotics for a 4-week period significantly reduced overall cognitive reactivity to depression and in particular aggressive and ruminative thoughts	[23]
<i>L. helveticus</i> R0052 + <i>B. longum</i> R0175	3x 10 <sup>9</sup> CFU	30 days	Hopkins Symptom Checklist-90; Hospital Anxiety and Depression Scale; Perceived Stress Scale; Coping Checklist; Urinary free cortisol; Statistical analyses	Consumption of the PF containing <i>L. helveticus</i> R0052 and <i>B. longum</i> R0175 in combination mitigated psychological distress without displaying any adverse event.	[22]

## Autism

Autism spectrum disorders (ASD, autism spectrum disorders) comprise a set of complex neurodegenerative disorders characterized by deficits in the ability to communicate and interact socially [12, 24]. A significant subset of children with ASD have gastrointestinal disorders, including constipation, diarrhea, bloating, abdominal pain, and excessive gas production, as well as increased intestinal permeability and altered gut microbiota composition, which, in the absence of communication skills, can exacerbate behavioral disorders [12, 24, 25, 26].

It has been shown that the amount of serotonin produced from tryptophan is decreased in the course of ASD. The intestinal microbiota imbalance reduces the tightness of the intestinal barrier, which results in activation of the lymphatic tissue within the gastrointestinal tract. Secreted mediators of the inflammatory response

lead to increased tryptophan participation in the kinurenic pathway, which can lead to the induction of oxidative stress and neurotoxic processes in the body.

Dietary modification in individuals with ASD to restore the normal composition of the gut microbiota is very difficult to achieve, due to the disorders that accompany individuals with autism. The vast majority of people with ASD have a sensory integration disorder, meaning that they have poor perception of specific colors or textures. Eating only foods and dishes of a particular color or texture would lead to a reduction in meal variety. Some work confirms that supplementation has led to a reduction in the intensity of behavioral disorders. It has also been shown that probiotic therapy minimized gastrointestinal abnormalities, which contributed to a reduction in behavioral deficits [27, 28] (Table 3).

**Table 3.** Probiotics in human models of ASD

Strain names	Dosage	Duration of intervention	Surveys used to evaluate primary outcome	Outcome	Refs
VSL#3 (a mixture of live cells of <i>Lactobacillus delbrueckii</i> subsp. <i>Bulgaricus</i> , <i>L. acidophilus</i> , <i>B. breve</i> , <i>B. longum</i> , <i>B. infantis</i> , <i>L. paracasei</i> , <i>L. plantarum</i> , <i>S. thermophiles</i> )	$9 \times 10^{10}$ CFU/g of viable, lyophilized bifidobacteria, $8 \times 10^{10}$ lactobacilli and $20 \times 10^{10}$ streptococci	5 months of treatment period (4 weeks of initial treatment + 4 months of follow up treatment); 10 months of follow up period	Autism Diagnostic Observation Schedule-2 (ADOS-2) assessment	Improvement in autistic core symptoms	[27]
<i>B. longum</i> , <i>L. rhamnosus</i> , <i>L. acidophilus</i>	$1 \times 10^8$ CFU per gram; 5 g per day	3 months	Autism Treatment Evaluation Checklist; The Gastrointestinal Severity Index; Statistical analysis	Reduce the severity of ASD symptoms	[28]

### Alzheimer's disease

AD (Alzheimer's disease, Alzheimer's disease) is a progressive neurodegenerative disorder that leads to gradual loss of memory and cognitive function and impairment. The cause of Alzheimer's disease is unknown, and the main risk factor is age. Only about 5% of cases have a genetic basis, and the vast majority are of idiopathic origin. The characteristic symptoms of AD are a decrease in the number of neurons, accumulation of senile plaques (which are extracellular deposits of amyloid; a harmful protein) in the extracellular space of the brain and meninges, and neurofibrillary tangles (which are located inside neurons and are a complex of hy-

perphosphorylated tau protein, the amount of which is directly proportional to the severity of AD symptoms) in the intracellular space [29, 30]. Acute and chronic neuroinflammation is one of the key elements in amyloid accumulation and progression of Alzheimer's disease [31]. Many studies have shown that oral supplementation of *B. breve* A1 used in cognitively impaired participants had a positive effect on memory function [32, 33, 34] (Table 4 and 5). In this situation, pro/prebiotics, such as lactic acid bacteria and *Bifidobacterium*, have attracted attention as tools for suppressing neuroinflammation. However, data on the therapeutic effects of probiotics and prebiotics in Alzheimer's disease are not extensive at present [31].

**Table 4.** Probiotics in rodent models of AD

Strain names	Dosage	Duration of intervention	Surveys used to evaluate primary outcome	Outcome	Refs
<i>Bifidobacterium breve</i> A1	$5 \times 10^8$ CFU/ml; 0.2ml per day	6 days	Y maze test; Passive avoidance test; Physiological analyses; RNA sequencing (RNA-seq) analysis; Microbiota analysis; SCFA analysis; Statistical analysis	improved cognitive dysfunction suppressed the expression of inflammation and immune-reactive genes induced	[35]

**Table 5.** Probiotics in human models of AD

Strain names	Dosage	Duration of intervention	Surveys used to evaluate primary outcome	Outcome	Refs
200 ml/day probiotic milk containing <i>Lactobacillus acidophilus</i> , <i>Lactobacillus casei</i> , <i>Bifidobacterium bifidum</i> and <i>Lactobacillus fermentum</i>	2 × 10 <sup>9</sup> CFU/g	12 weeks	Assessment of Anthropometric Measures; Mini-Mental State Examination (MMSE); Assessment of Biochemical Parameters	Improvement in patients MMSE (Mini-Mental State Examination) scores	[36]
<i>Bifidobacterium breve</i> A1 (MCC1274)	2x10 <sup>10</sup> CFU	16 weeks	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS); The Japanese version of the MCI Screen (JMCI)	Significant improvement of cognitive functions	[34]

### Anorexia nervosa

AN (anorexia nervosa, mental anorexia nervosa) is a disorder that belongs to the eating disorders group. The incidence of this disorder among women is 10 times higher than among men. The greatest risk of developing the disorder is between the ages of 14 and 18. AN is manifested by the desire to achieve a large reduction in body weight and a strong fear of gaining weight, and thus people suffering from anorexia nervosa use many methods such as: low-calorie diets, intensive exercise, and taking laxatives. Anorexia is diagnosed when the sufferer reach-

es a body weight at least 15% lower than expected for age and height [37]. The causes of AN can range from biological to genetic to cultural and familial factors [38]. Anorexia nervosa is characterized by irreversible neurological changes, endocrinological and metabolic disorders, caused by a very rapidly progressive cachexia [37].

In the case of mental anorexia nervosa, the amount of scientific data on the use of probiotics for this disorder is limited. Studies show that probiotic therapy can serve as an adjunctive therapy in the nutritional treatment of anorexia (Table 6).

**Table 6.** Probiotics in human models of anorexia nervosa

Strain names	Dosage	Duration of intervention	Surveys used to evaluate primary outcome	Outcome	Refs
375 g/d of yogurt Containing <i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i> and <i>Streptococcus thermophilus</i>	10 <sup>7</sup> -10 <sup>8</sup> CFU/ml; 375 g of yogurt per day	10 weeks	flow cytometry; enzyme-linked immunosorbent assay (ELISA); Statistical analysis	Improvement of nutritional status	[39]

### SUMMARY

1. A multi-species probiotic containing *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus*

*salivarius* W24, and *Lactococcus lactis* W19 and W58 was shown to have positive anti-stress effects in humans. It was also shown that the combination of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 reduced the severity of depressive symptoms in humans.

2. It was shown that after the use of a multi-species probiotic containing *Lactobacillus delbrueckii* subsp. *Bulgaricus*, *L. acidophilus*, *B. breve*, *B. longum*, *B. infantis*, *L. paracasei*, *L. plantarum*, *S. thermophiles* led to improvement in autistic core symptoms. In addition, the combination of probiotics *B. longum*, *L. rhamnosus*, *L. acidophilus* decreased the severity of ASD symptoms.
3. A multi-species probiotic containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum* i *Lactobacillus fermentum* led to improvements in patients' scores on the MMSE (Mini-Mental State Examination) scale. The use of probiotic *Bifidobacterium breve* A1 led to improved cognitive function.
4. In the case of mental anorexia nervosa, a multi-strain probiotic containing *Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus* led to improved nutritional status, with concurrent nutritional therapy.
5. At the same time, the literature review shows that despite ample evidence of links between neurodevelopmental, emotional, and neurodegenerative disorders and gut microbiota imbalances, at this stage of research it is not possible to precisely understand the mechanisms linking these disorders, which means that further observations and related analyses are necessary.

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