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REVIEW ARTICLE

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The impact of probiotic supplementation on depressive symptoms: a systematic review of clinical trials

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ABSTRACT

Background: Over the past few years, there has been a growing interest in comprehending the complex relationship between gut microbiota and mental health, particularly depression. **Aims:** The systematic review aimed to evaluate the efficacy of probiotic supplementation in alleviating depressive symptoms. **Methods:** A comprehensive literature search was conducted using the PubMed and Scopus databases, focusing on studies published between 2013 and 2024. The MESH terms "Probiotics", "Psychobiotics", "Probiotic Treatment outcomes", and "Probiotic Consumption" were used to describe the intervention, while the MESH terms "Depression", and "Depressive Disorders" were used to describe the outcome. Only papers published in English were included and there was also a restriction in date for all the included studies (2013 – 2024). **Results**: Eighteen studies met the inclusion criteria for this systematic review, comprising 14 randomized controlled trials (RCTs) and 4 case-control studies (CTs). The intervention period ranged from 1 to 12 months. While most studies included both male and female participants, four studies exclusively enrolled women. The age range of participants exceeded 16 years. Overall, the majority of studies (N = 12) reported an improvement in depressive symptoms following probiotic administration for a specified duration. However, 6 studies did not demonstrate significant effects. **Conclusion:** While the majority of trials indicated suggest a potential benefit of probiotics in alleviating depressive symptoms, several had no meaningful benefit, presumably because of differences in strains, dosages, intervention durations, participant factors, and end measures. the evidence remains inconclusive due to the heterogeneity of study designs and outcomes. This underscores the necessity for further studies to explore the role of probiotics in mental health and to establish more definitive guidelines for their use in clinical practice.

Keywords: Probiotics, gut microbiome, depression, depressive symptoms, mental health.

ARTICLE INFORMATION

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1 Introduction

The World Health Organization estimates that depressive disorders are among the most common mental illnesses worldwide and affect about 5% of the adult population, which is approximately 280 million people, in 2019 (World Health Organization, 2022. This growing prevalence has made some researchers attribute depression as a disorder greatly associated with lifestyles characteristic of modern times, hence its growing concern (Hidaka, 2012 .

One of the important domains of exploration involved in the elucidation of neurochemical bases of depression has something to do with the elucidation of gamma-aminobutyric acid participation (GABA. GABA constitutes one of the most abundant neurotransmitters in the brain, playing a critical role in controlling inhibitory synaptic transmission that accounts for approximately 40% of adults. In the central nervous system, GABA is synthesized from glutamic acid through the action of the enzyme glutamic acid decarboxylase. GABA exerts its inhibitory effects through two receptor types: the ionotropic GABAA receptor and the metabotropic GABAB receptor, involved in fundamental physiological processes that range from the regulation of sleep to the maintenance of mood stability.

Disturbances in GABAergic transmission have indeed been implicated in the etiology of Major Depressive Disorder. A

decreased concentration of GABA within the brain, impaired functioning of GABAergic interneurons, and changes in receptor expression and function may thus be said to contribute to the onset and course of depression (Liwinski et al., 2023; Luscher & Fuchs, 2015. Symptoms of depression may commonly include moodiness, sadness for much of the day, a loss of interest in activities, changes in appetite and sleep, feeling guilt or worthlessness, and, in severe states, suicidal thoughts (APA Dictionary of Psychology, n.d. .

Recent research also points out that fermented foods may be relevant to mental health, especially as a source of GABA. Fermented food has probiotics, and some varieties are even called "psychobiotics" because they have beneficial effects on one's mental health (Sanchez-Villegas & Martínez-González, 2013. Probiotics are living microorganisms that can be incorporated into food, used as dietary supplements, or naturally found in fermented foods (NIH, 2022. O ne of the primary functions of probiotics is to act as a protective barrier in the (NIH, 2022 intestine against harmful bacteria, preventing their colonization in the gut microbiota (Butel, 2014. Additional ly, probiotics can boost the functionality of the gut mucosal barrier and adjust the immune system. Notably, more than 70% of the mucosal immune system is presented as small foci of lymphocytes and plasma cells scattered widely throughout the lamina propria of the gut wall (Rivera & Lennon-Duménil, 2023.

Based on the research, probiotics have attracted attention due to their potential influence on depression. In particular, laboratory studies have reported encouraging results regarding the therapeutic effects of probiotics on depression (Cichońska et al., 2023. Moreover, human studies have indicated that probiotics may alleviate symptoms of depression, particularly in individuals who suffer from gastrointestinal disorders and have a higher propensity for depression and anxiety than the average population does (Mörkl et al., 2020. A meta -analysis study showed that daily probiotic supplementation lessened anxiety among pregnant women but with no effect on depressive symptoms (Desai et al., 2021. Another meta - analysis investigation compared the impact of probiotic therapy on psychological changes among healthy controls, cases with psychiatric symptoms, and central functioning revealed no significant changes in the depression scores of the probiotic when compared with the respective scores of the control group (Le Morvan de Sequeira et al., 2022. With increasing evidence regarding the association between gut health and mental well-being, further gut-brain axis exploration concerning the function of probiotics in the treatment of depression is imperative.

The gut-brain axis is a communication system that physically and biochemically connects the gut and the brain, enabling bidirectional interactions that impact upon human psychology and behavior (Appleton, 2018; Generoso et al., 2020. However, additional research is deemed essential to gain a comprehensive understanding of the gut microbiome-brain axis. Specifically, the association between gut microbiota and mental illnesses requires further investigation. Notably, conflicting results have been found in earlier research examining the role of probiotic supplementation in mental illnesses, and there are still a lot of questions in this area (Desai et al., 2021; Mörkl et al., 2020. Henc eforth, this comprehensive analysis aims to clarify the mechanism of functioning of the gut microbiome-brain axis and to systematically examine, select, and assess randomized clinical studies that studied the effects of probiotic supplementation on depression.

2 Methods

2.1 Research method and requirements for eligibility

An extensive search in the PubMed and Scopus databases used MESH terms "Probiotics", "Psychobiotics", "Probiotic Treatment outcomes", and "Probiotic Consumption" to describe the intervention, while the MESH terms "Depression", and "Depressive Disorders" were used to describe the outcome. Additionally, the references in the selected articles were manually examined. Two researchers did an independent literature search from 2023 to 2024. Only English-language publications were included in the search, and the research included date constraints (2013 – 2024 to

Table 1. Search strategy in PubMed and Scopus databases

	Keywords	Number of Searches	Studies retrieved in PubMed	Studies retrieved in Scopus
Probiotics – Intervention	(((Probiotics [Title]) OR (Psychobiotics [MeSH Terms])) OR (Probiotic Treatment outcomes [MeSH Terms])) OR (Probiotic Consumption [MeSH Terms])	#1	9,602	30,256
Mental Health (Depression)- Outcome	(Depression [Title])) OR (Depressive Disorders [MeSH Terms]))	#2	202,641	175,423
	#1 + #2	#3	89	126

ensure that the most recent data were included. Discrepancies between reviewers were resolved collaboratively with the assistance of a third author. The search approach utilized is shown in Table 1.

Inclusion criteria for eligibility included all individuals experiencing depressive symptoms or diagnosed with depression, regardless of age, gender, or ethnicity. Probiotic supplementation was the intervention/exposure under study, whereas the changes in depression or depressive symptoms were the primary outcomes, The control group represents the patients with depression receiving placebos. Only clinical trials (CTs and randomized controlled trials (RCTs were considered in this paper. On the other hand, case reports, published conference abstracts, narrative reviews, and dissertations were not included.

2.2 Study selection and data extraction

The titles and the abstracts retrieved from electronic searches were independently evaluated by two reviewers, and full-text articles from selected studies that satisfied the eligibility criteria were retrieved. Subsequent to the initial phase, the same assessors conducted a secondary review to arrive at a final decision. Any discrepancies between the reviewers were resolved with the assistance of a third author. The information derived from each analysis consisted of the subsequent components: year, country of origin, and author; study design and primary outcomes; intervention utilized; and primary discoveries.

In regard to study selection, a total of 215 articles were identified (89 were obtained through PubMed and 126 through Scopus. Following the elimination of irrelevant and duplicate studies, a critical assessment of a total of 209 studies was carried out by analyzing the Title and Abstract of each article. Of these, 178 studies were excluded from the analysis as they did not satisfy the eligibility criteria, either due to lack of relevance to the research question or absence of probiotics administration in the intervention. Subsequently, the remaining 31 studies were assessed based on the full text of each article. Thirteen of them were eliminated since they didn't fit the requirements for admission. As a result, the current study included the remaining 18 trials. The selection procedure is presented in Figure 1.

2.3 Quality assessment

Two independent reviewers assessed the included studies' methodological quality. The Jadad score was developed to evaluate randomized control trials (RCTs based on randomization, blinding, and participant dropout rates. This scoring system assigns a final score ranging from 0 to 5 points. A score of ≥ 3 is considered "high quality," while a score of ≤2 is categorized as "low." (Jadad et al., 1996.

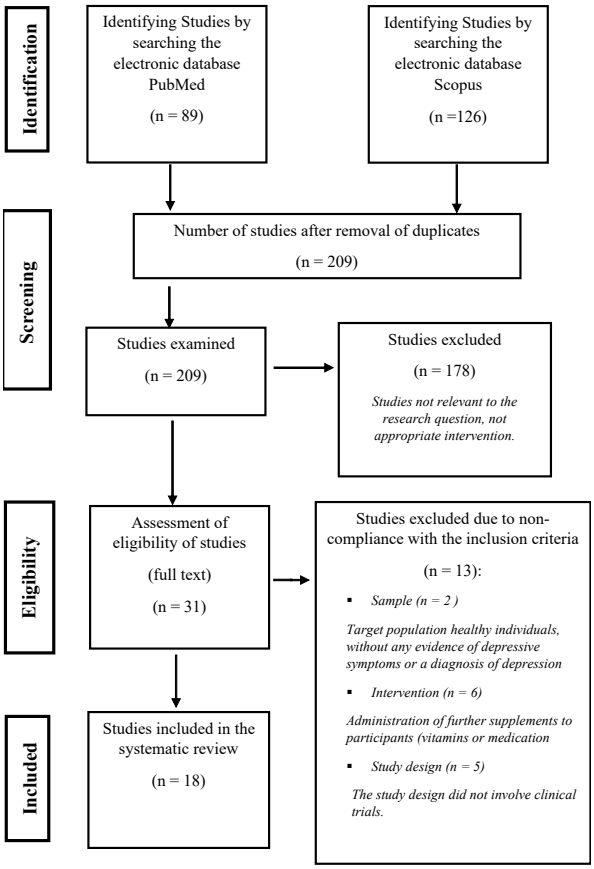

Figure 1. PRISMA flow diagram

3 Results

In the present review 18 studies met the inclusion criteria; 4 RCTs and 14 CTs with patients of both sexes, except 4 studies, with ages of 16 years and over, in which the patients were exclusively women. The duration of intervention with probiotics varied from one to 12 months. Upon the receipt of the bacteria probiotics, depression symptoms were reduced in 66% of cases (12 out of 18), with no beneficial changes among the remaining patients. Methodological Assessment Quality scored 14 studies 5/5, one study, 4/5, and three studies 3/5, according to Jadad's scale score.

3.1 Clinical studies reporting improvement in cases of depression following administration of probiotics

Obese Tunisian adults over 18 years were treated daily with a combination of Bifido, Lactocasei bacillus, and Streptococcus probiotic bacteria at a dosage of 1010 CFU for one month (Ben Othman et al., 2023). The one-month intake of probiotics was associated with significant improvement in

Table 2. Assessment of the methodological quality of studies

Authors	Criteria						
	Randomization	Suitability of	Double randomization blindness method	Suitability of double blindness	Withdrawal report	Total Quality Score	Results
Ben Othman et al., 2023	√	√	-	-	√	3/5	high
Schaub et al., 2022	√	√	√	√	√	5/5	high
Tian et al., 2022	√	√	√	√	√	5/5	high
Browne et al., 2021	√	√	√	√	√	5/5	high
Ho et al., 2021	√	-	√	-	√	3/5	high
Shafie et al., 2021	√	√	√	√	√	5/5	high
Zhang et al., 2021	√	√	√	-	√	4/5	high
Kim et al., 2021	√	√	√	√	√	5/5	high
Dawe et al., 2020	√	√	√	√	√	5/5	high
Reiter et al., 2020	√	√	-	-	√	3/5	high
Chahwan et al., 2019	√	√	√	√	√	5/5	high
Kazemi et al., 2019	√	√	√	√	√	5/5	high
Rudzki et al., 2019	√	√	√	√	√	5/5	high
Majeed et al., 2018	√	√	√	√	√	5/5	high
Pinto-Sanchez et al., 2017	√	√	√	√	√	5/5	high
Romijn et al., 2017	√	√	√	√	√	5/5	high
Slykerman et al., 2017	√	√	√	√	√	5/5	high
Akkasheh et al., 2016	√	√	√	√	√	5/5	high

depression and anxiety and a decrease in Epworth score and the HADS scale ($p < 0.05$) (Ben Othman et al., 2023).

The daily administration of *Bifidobacterium breve* at a dosage of 1010 CFU to Chinese patients with major depression disorder (MDD) and gastrointestinal symptoms for one month led to significant antidepressant-like effect using Hamilton psychometric Depression Rating scale-24 (HDRS-24), Montgomery-Asberg Depression Rating Scale (MADRS), Brief Psychiatric Rating Scale (BPRS), and Gastrointestinal Symptom Rating Scale (GSRS) as well in the serum concentration of tryptophan metabolites, serotonin neurotransmitter (5_HT), cortisol, Tumor necrotic factor (TNF-α) and interleukin- β (IL-β) and gut microbiome composition compared to the respective results ($P<0.05$) obtained with the placebo group (Tian et al., 2022). In a further clinical trial, Swiss patients over 18 years with recurrent depression were treated daily with 8 multi-strain probiotic bacteria supplements (Vivomixx®, providing daily 900 billion CFU. The authors reported that the one-month intake of probiotics caused a significantly stronger decrease in HAM-D scores compared to the placebo group from baseline to post-intervention ($p < 0.05$) and from baseline to follow-up ($p < 0.01$) (Figure 1). At follow-up, 80% of patients in the probiotics group and 48% of patients in the placebo group showed a reduction in HAM-D scores (greater than 57%), indicating a strong statistical trend ($\chi 2(1,45) = 3.57$, $p > 0.05$) (Schaub et al., 2022).

Fermented beverage dairy preparation containing a dosage of 1010 CFU *Lacticaseibacillus paracasei* Shirota, was served daily to a group of Chinese patients between 18 and 60 years old diagnosed with depression and suffering also from constipation (Rome IV Criteria) (Akkasheh et al., 2016). The conditions of the patients belonging to both groups and control and in the intervention improved significantly at the termination of the 9 weeks of the trial based on reduced Hamilton Depression Rating Scale (HAMD) scores. Most notable was a decrease in the abundance of gut microbiota related to mental illness, such as Rikenellaceae_RC9_gut_group, Sutterella, and Oscillibacter (Zhang et al., 2021).

Table 3. Main characteristics and findings of the studies included in the systematic review

Ref No	Patients	Probiotics, Duration	Primary Outcomes, Secondary outcomes
Ben Othman et al., 2023	N: 45; 48.7 y, F+M	*B. longum* + *L. helveticus* + *L. lactis* + *S. thermophilus*, 10*10^9 CFU /d; duration 1 month	↓ Depressive symptoms
Schaub et al., 2022	N: 47; 39.4 y, F+M	*B. breve* + *B. Lactis* + *L. Acidophilus* + *L. Plantarum* + *L. Paracasei* + *L. Helveticus* + *S. thermophilus* 900 billion CFU/d; duration 1 month	↓ Depressive symptoms In HAM-D, BDI
Tian et al., 2022	N: 45; 51.3 y, F+M	B. breve, 10^{10} cfu/d, duration 1 month	↓ Depressive symptoms associated with gastrointestinal disorders.
Browne et al., 2021	N: 40; 29.6 y, F	*B. bifidum* W23 + *B. lactis* W51 + *B. lactis* W52 + *L. acidophilus* W37+ *L. brevis* W63 + *L. casei* W56 + *L. salivarius* W24 + *Lc. lactis* W19 + *Lc. lactis* W58, 2.5*10^9 CFU/d; duration 2 months	Inconclusive findings
Ho et al., 2021	N: 40; 25.4 y, F+M	PS128, 3*10^{10} CFU/ 2*daily; duration 1 month	↓ Depressive symptoms, fatigue ↑Brain activity, deep sleep quality
Shafie et al., 2022	N: 66; 51.8 y, F	*L. bulgaricus* + *S. thermophilus* + *B. lactis* + *L. acidophilus*, 10^8 CFU/d; duration 6 weeks	No significant change in depressive symptoms ↓ Anxiety, tension
Zhang et al., 2021	N: 69; 45.8 y, F+M	*L. paracasei Shirota*, 10^8 CFU/d; duration 11 weeks	↓ Depressive symptoms
Kim et al., 2021	N: 53; 71.5, F+M	*B. bifidum* BGN4 + *B. longum* BORI, 10^9 CFU/d; duration 3 months	No significant change in depressive symptoms
Dawe et al., 2020	N: 164; 29.7 y, F	L. rhamnosus GG + *B. lactis* BB12, 6.5*10^9 CFU/d; duration 6 months	No significant change in depressive symptoms
Reiter et al., 2020	N: 82; 41.5 y, F+M	*L. casei* W56 + *L. acidophilus* W22 + *L. paracasei* W20 + *B. lactis* W51 + *L. salivarius* W24 + *L. lactis* W19 + *L. plantarum* W62 + *B. lactis* W52 + *B. bifidum* W23, 7.5*10^9 CFU/d; duration 1 month	↓ Depressive symptoms in mild to moderate inflammation
Chahwan et al., 2019	N: 71; 36 y, F+M	*B. bifidum* W23 + *B. lactis* W51 + *B. lactis* W52 + *L. acidophilus* W37 + *L. brevis* W63 + *L. casei* W56 + *L. salivarius* W24+ *Lc. lactis* W19 + *Lc. lactis* W58, 2.5*10^9 CFU/d; duration 1 year	No significant change in depressive symptoms
Kazemi et al., 2019	N: 110; 36.4 y, F+M	*L. helveticus* + *B. Longum*, 10^9 CFU/d; duration 2 months	↓ Depressive symptoms
Rudzki et al., 2019	N: 60; 39 y, F+M	SSRI + *L. plantarum* 299v, 10*10^9 CFU/2*daily; duration 2 months	↑ Cognitive skills in patients with MDD
Majeed et al., 2018	N: 40; 40.3 y, F+M	*B.coagulans* MTCC 5856, 2*10^9 CFU/d; duration 3 months	↓ Depressive symptoms
Pinto-Sanchez et al., 2017	N: 44; 46.5 y, F+M	BL, 10^{10} CFU/d + maltodextrin; duration 6 weeks	↓ Depressive symptoms ↓ IBS symptoms
Romijn et al., 2017	N: 79; 35.8 y, F+M	*L. helveticus* + BL, 3*10^9 CFU/d; duration 2 months	No significant change in depressive symptoms
Slykerman et al., 2017	N: 423; 33.5 y, F	*L. rhamnosus* HN001, 6*10^9 CFU/d; duration 10 months	↓ Depressive symptoms
Akkasheh et al., 2016	N:40, 38.3 y, F+M	*L. acidophilus* + *L. casei* + *B. bifidum*, 2*10^9 CFU/d; duration 2 months	↓ Depressive symptoms & Oxidative stress ↑ Insulin function

MDD: Major Depressive Disorder; HDRS/ HAMD: Hamilton Rating Scale for Depression; CFU: colony forming unit, BDI: Beck Depression Inventory; IBS irritable bowel syndrome

A clinical study coming out of Taiwan was carried out on patients aged 20 – 40 years of age with self-reported patients with subjective depressive symptoms, anxiety, and sleep disorders, and miniature-polysomnography receiving daily capsules containing 3x10^{10} CFU PS128 for 30 days. The authors reported that all outcomes were comparable at baseline between the 2 groups. Following the 30 – day intake of PS128, improved depressive symptoms and these improvements were related to changes in brain waves and sleep maintenance (Ho et al., 2021). Iranian patients aged 18 to 50 years with, mild to moderate major depression, who were taking anti-depressant drugs: were divided randomly

into intervention groups receiving a daily sachet containing $7.5*10^9$ CFU/g with a multispecies probiotic drink consisting of *Lacticaseibacillus Helveticus* and *Bifidobacterium longum*. At the end of the 30 – day intervention, the reduction in the BDI score showed a significant difference between the and the probiotic-treated group ($p < 0.04$) (Kazemi et al., 2019). In the pairwise analysis, the mean BDI score significantly decreased in the probiotic group compared to the placebo ($p=0.008$) and control groups significantly improved in psychological parameters (BDI: $p < 0.05$; HAMD: $p < 0.05$). The change in the tryptophan/isoleucine ratio was significant between the two study groups ($p = 0.026$) (Kazemi et al., 2019). The research conducted by Kazemi et al. (2019) involved an 8 – week intervention with a daily dosage of *Bifidobacterium longum* and *Lactobacillus helveticus*. When compared to the placebo group, the BDI score decreased significantly ($p < 0.05$). Additionally, Rudzki et al.'s study (intervention 8 weeks; 2 capsules daily, $10x10^9$ CFU of SSRI and probiotic strain Lactobacillus Plantarum 299v) discovered that probiotic supplementation enhanced patients' cognitive abilities by lowering their kynurenine concentration (Repeated Measures ANOVA: $p = 0.005$ & Bonferroni post hoc: $p < 0.05$). Using the HAM-D and MADRS scales, Majeed et al.'s (2018) study (intervention lasting three months and daily dosage of *B. coagulans* MTCC 5856, $2x10^9$ CFU/g) showed a substantial ($p < 0.05$) decrease in depressive symptoms in the intervention group as compared to the placebo one. Pinto-Sanchez et al. (2017) found that a 6-week intervention with BL 1.0E+10 CFU/g powder and maltodextrin reduced mild-to-moderate depression symptoms by 2 or more points on the HAD scale ($p < 0.05$).

Slykerman et al. (2017) found that a 10 – month intervention with *Lactobacillus rhamnosus* HN001 at a dose of $6x10^9$ CFU/g resulted in a significantly lower depression score ($p < 0.05$) compared to the control group. Akkasheh et al. (2016) found that a 2-month intervention with Lactobacillus acidophilus, *Lactobacillus casei*, and *Bifidobacterium bifidum* at a dosage of $2x10^9$ CFU/g improved BDI scores for persons with major depressive disorder ($p < 0.05$).

3.2 Studies with negative or no effect of probiotics on depression

Annex Shafie et al. Study (2022) (intervention 6 weeks; daily intake of 100 g, $1x10^8$ CFU/g; L. bulgaricus and Streptococcus thermophilus, g bifidobacterium lactis and L. Acidophilus) revealed no discernible difference between the controls and the individuals receiving probiotic treatment ($p = 0.886$). The quality of life in postmenopausal women was found to be positively influenced by the consumption of probiotic yogurt, resulting in decreased levels of anxiety and tension. Nevertheless, no significant changes were noted in terms of depression ($p = 0.433$). Similarly, on the Edinburgh Postnatal Depression Scale, Browne et al. (2021) (intervention 2 months; multi-species probiotic combination, $2.5x10^9$ CFU/g per day) found that the intervention and control groups did not exhibit any statistically significant alterations (ANOVA: $p > 0.05$). The treatment had an impact on the participants' mental and cognitive health, according to a study by Kim et al. (2021) (intervention 3 months; 4 capsules daily of Bifidobacterium bifidum BGN4 and *Bifidobacterium longum* BORI, $1×10^9$ CFU/g). On the other hand, the effect of the intervention on depressive symptoms did not yield significant statistical results ($p = 0.12$). The study by Dawe et al. (2020) produced similar results (intervention 6 months; *Bifidobacterium lactis* BB12, $6.5×10^9$ CFU/g, and *Lactobacillus rhamnosus* GG), where depression ratings were consistent and did not vary across the groups ($p = 0.217$). Moreover, Chahwan et al. (2019) study, which included a 12-month intervention and 2 g of a frozen probiotic powder mixture containing 9 strains and $2.5×10^9$ CFU/g, showed no significant main effect of probiotics on depression and had a non-significant p-value ($p = 0.64$ in the BDI scale). Lastly, no discernible decrease in depression symptoms ($p = 0.99$) was observed in the study by Romijn et al. (2017) (intervention 8 weeks; *Lactobacillus helveticus* and *Bifidobacterium longum*, ≥ $3×10^9$ CFU/1.5 g). When probiotics are employed as the primary therapy in a symptomatic sample, researchers believe it will take longer than 8 weeks to cause mood improvements.

4 Discussion

Probiotics generally affect the mucus layer, the intestinal lymphoid tissue, and the epithelial layer of the human gastrointestinal tract in three different ways (Sánchez et al., 2017). The overall makeup and metabolic activity of the gut microbiota are influenced by these interactions (Hemarajata & Versalovic, 2013). Probiotics function in several ways, such as enhancing the intestinal mucosal barrier, altering the host's gut microbiota, and influencing the immune system. They improve the epithelial barrier and build the mucus layer, preventing direct contact with gut bacteria (Butel, 2014; Glavanou & Kokorogiannis, 2022). Probiotics interact with host intestinal cells mainly at the surface of the intestinal barrier, including the intestinal epithelium and the underlying lamina propria (Gou et al., 2022). This interaction is essential for maintaining intestinal integrity and influencing immune responses, particularly in the gut.

Probiotics also affect the immune system, particularly in the small intestine, which houses more than 70% of immune cells (Butel, 2014). Moreover, a critical aspect of the influence of probiotics on mental well-being is the Gut-Brain Axis, a communication pathway that operates in both directions connecting the stomach and the brain. This axis involves intricate connections that impact physiological functions and behaviors between the intestinal and central nervous systems.

As a result, probiotics can manipulate the Gut-Brain Axis, leading to potential improvements in mood and mental health through alterations in gut microbiota and microbial metabolites (Sarkar et al., 2018).

Recent systematic reviews have shed light on how probiotics affect neuronal functions and mental health. According to a recent systematic review and meta-analysis, probiotics can affect the central nervous system (CNS) functions by improving gut-brain connections and modifying neuroinflammatory responses. These effects are seen in psychiatric symptoms (e.g. depression). Research demonstrates that probiotics can affect neurotransmitter systems that are important for mood regulation, like GABA and serotonin, which are vital for neural communication. These findings demonstrate how probiotics may improve mental health by modifying gut microbiota and lowering inflammatory responses in the system (Le Morvan de Sequeira et al., 2022). Along this line, Bagga et al. (2018) found that probiotics can alter gut microbiota to produce detectable changes in emotional brain signatures. Their study found that probiotics affect the prefrontal cortex and amygdala, two areas of the brain that are essential in emotional processing. This agrees with the hypothesis that modification of the gut microbiome by the administration of probiotics may lead to observable changes in psychiatric symptoms, pointing toward a direct relationship between gastrointestinal bacteria and brain function. Also, Tillisch et al. (2013) have demonstrated that eating fermented milk containing probiotics affects brain activity, particularly in areas controlling emotional and sensory processing. These are all studies that indicate the potential of probiotics as a non-pharmacological way to affect brain function and improve mental health with dietary changes (Tillisch et al., 2013).

To assess the impact of probiotic supplementation on individuals with depression, a thorough review was conducted, incorporating a total of eighteen clinical studies. According to the results, the majority of the studies show that probiotics can reduce depressive symptoms after a certain amount of time, while the remaining studies (n = 6) showed that there was no difference in the two groups' levels of depression symptoms after the intervention. Numerous factors, such as research design, intervention specificity, and participant characteristics, may be responsible for the differences in results between the two groups of studies, those reporting significant results and those indicating no significant impact of probiotics on depression. The studies that did not produce positive results employed various probiotic strains, variable doses, and intervention periods ranging from 1 to 6 months. This variation in probiotic strains and dosage may be the cause of the lack of consistent favorable effects. A few of the studies that yielded non-significant results only had relatively short intervention periods (one to two months). For instance, the duration of the interventions in Shafie et al. (2021), Browne et al. (2021), and Kim et al. (2021) was 6 weeks, 2 months, and 3 months, respectively. Conversely, a number of trials with positive results had longer intervention periods (6 weeks to 10 months). The length of the intervention could affect how quickly probiotics improve symptoms of depression. The lack of effect that probiotic supplementation had on the two groups of participants may have resulted from the individuals' self-efficacy, which was demonstrated by their regular probiotic consumption, appointment scheduling, and other routine actions meant to lessen depressed symptoms (Chahwan et al., 2019). The results of previous reviews on this subject are consistent with the findings of the current systematic review. Our findings align with those of the latest systematic reviews conducted by Halemani et al. (2023) and Siroska et al. (2023), which explored the effects of probiotics on the microbiome and mental health of infants. Their findings indicated that while there is a favorable correlation between probiotic administration and a reduction in depressive symptoms, specific inferences could not be made. Additionally, Alli et al. (2022) and Sanada et al. (2020) found substantial variations in the makeup of the gut microbiota between the control and treatment groups.

The primary goal of these studies was to investigate the disparities in the composition of microbiota between individuals who are in good health and those who have been diagnosed with Major Depressive Disorder (MDD) or exhibit symptoms of depression. Using the Beck Depression Inventory (BDI) and the State-Trait Anxiety Inventory (STAI), El Dib et al. (2021) conducted a comprehensive review and meta-analysis of 16 RCTs, which demonstrated a substantial decrease in the symptoms of anxiety and depression in patients receiving probiotic treatment. Our results are in line with those of Huang et al. (2016) and Wallace et al. (2017), who assessed the data on the relationship between probiotics and depression and discovered that probiotics may lower depression scale scores.

In an evaluation of probiotic supplementation in individuals with anxiety and depression, Pirbaglou et al.'s (2016) review, discovered that probiotic supplementation lowers stress and may have psychological benefits. In contrast to our results, a prior thorough analysis of nine RCTs looked at how probiotic administration affected depression and other psychological symptoms, but it revealed no discernible changes between the groups (Minayo et al., 2021). By comparison, the findings of Liu et al.'s (2019) investigation, which examined the efficacy of probiotics and prebiotics in addressing anxiety and depression, did not identify any significant difference between the placebo and intervention groups. Once again, this underscores the need for additional research. Nevertheless, considering the heterogeneous nature of the data, variations in study designs, inadequate reporting in certain studies, ambiguity regarding extraneous factors, and the

acknowledged need for further research, the researchers approach drawing definitive conclusions with caution.

Strengths and limitations of the systematic review

There are various advantages to this systematic review. To be more precise, each included study was assessed with outstanding methodological quality. Additionally, every study that was included was experimental (a CT or an RCT), meaning that the target group was quite narrow, and the intervention was very concentrated. The inclusion of studies from many nations is another advantage of this analysis.

However, some restrictions were also noted. Specifically, there isn't much research included, and the sample of the clinical trials isn't large either. Moreover, different research studies employed different outcome criteria to evaluate symptoms of depression. The varying results could have been caused by variations in these scales' sensitivity and specificity. Additionally, a wide range of probiotic strains, doses, and durations were employed in the study. There were differences in the subjects' ages, depression levels, and participation characteristics. Lastly, there was no meta-analysis done because of the results' significant heterogeneity and lack of generalizability.

5 Conclusion

This study highlights the advantageous effects of probiotics in managing depression symptoms. A significant deduction from these results is that the intake of probiotics leads to a reduction in depressive symptoms by enhancing the composition of gut microflora.

This paper underlined the gaps and ambiguities that exist around this topic. However, many points need to be clarified around this subject, so the following recommendations for future research are reasonable. Particularly, the appropriate dosage that should be recommended for consumption needs to be determined. Also, it's important to identify which strains produce the most optimal results, and the exact duration that the treatment should be implemented. Finally, it is of paramount importance to identify the mental disorders that are ultimately affected by this intervention.

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References

Akkasheh, G., Kashani-Poor, Z., Tajabadi-Ebrahimi, M., Jafari, P., Akbari, H., Taghizadeh, M., Memarzadeh, M. R., Asemi, Z., & Esmaillzadeh, A. (2016). Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. *Nutrition (Burbank, Los Angeles County, Calif.)*, *32*(3), 315–320. https://doi.org/10.1016/j.nut.2015.09.003 [Crossref] [Google Scholar] [PubMed] [Publisher]

Alli, S. R., Gorbovskaya, I., Liu, J. C. W., Kolla, N. J., Brown, L., & Müller, D. J. (2022). The gut microbiome in depression and potential benefit of prebiotics, probiotics and synbiotics: A systematic review of clinical trials and observational studies. *International Journal of Molecular Sciences*, *23*(9), 4494. https://doi.org/10.3390/ijms23094494 [Crossref] [Google Scholar] [PubMed] [Publisher]

APA Dictionary of Psychology. (n.d.). Retrieved September 27, 2024, from https://dictionary.apa.org/

Ahmad, N.-, Zuki, M. A.-M., Azahar, N. A.-, Khor, B. H.-, & Minhat, H. S.-. (2019). Prevalence and factors associated with sugar-sweetened beverage intake among undergraduate students in a public university in Malaysia. *Pakistan Journal of Nutrition: PJN*, *18*(4), 354–363. https://doi.org/10.3923/pjn.2019.354.363 [Crossref] [Google Scholar] [PubMed] [Publisher]

Appleton, J. (2018). The gut-brain axis: Influence of Microbiota on mood and mental health. *Integrative Medicine (Encinitas, Calif.)*, *17*(4), 28–32. [Google Scholar] [PubMed]

Bagga, D., Reichert, J. L., Koschutnig, K., Aigner, C. S., Holzer, P., Koskinen, K., Moissl-Eichinger, C., & Schöpf, V. (2018). Probiotics drive gut microbiome triggering emotional brain signatures. *Gut Microbes*, *9*(6), 486–496. https://doi.org/10.1080/19490976.2018.1460015 [Crossref] [Google Scholar] [PubMed] [Publisher]

Ben Othman, R., Ben Amor, N., Mahjoub, F., Berriche, O., El Ghali, C., Gamoudi, A., & Jamoussi, H. (2023). A clinical trial about effects of prebiotic and probiotic supplementation on weight loss, psychological profile and metabolic parameters in obese subjects. Endocrinology, Diabetes & Metabolism, 6(2), e402. https://doi.org/10.1002/edm2.402 [Crossref] [Google Scholar] [PubMed] [Publisher]

Browne, P. D., Bolte, A. C., Besseling-van der Vaart, I., Claassen, E., & de Weerth, C. (2021). Probiotics as a treatment for prenatal maternal anxiety and depression:

a double-blind randomized pilot trial. Scientific Reports, 11(1), 3051. https://doi.org/10.1038/s41598-021-81204-9 [Crossref] [Google Scholar] [PubMed] [Publisher]

Butel, M.-J. (2014). Probiotics, gut microbiota and health. Médecine et Maladies Infectieuses, 44(1), 1–8. https://doi.org/10.1016/j.medmal.2013.10.002 [Crossref] [Google Scholar] [PubMed] [Publisher]

Chahwan, B., Kwan, S., Isik, A., van Hemert, S., Burke, C., & Roberts, L. (2019). Gut feelings: A randomised, triple-blind, placebo-controlled trial of probiotics for depressive symptoms. Journal of Affective Disorders, 253, 317–326. https://doi.org/10.1016/j.jad.2019.04.097 [Crossref] [Google Scholar] [PubMed] [Publisher]

Cichońska, P., Kowalska, E., & Ziarno, M. (2023). The survival of psychobiotics in fermented food and the gastrointestinal tract: A review. Microorganisms, 11(4). https://doi.org/10.3390/microorganisms11040996 [Crossref] [Google Scholar] [PubMed] [Publisher]

Dawe, J. P., McCowan, L. M. E., Wilson, J., Okesene-Gafa, K. A. M., & Serlachius, A. S. (2020). Probiotics and maternal mental health: A randomised controlled trial among pregnant women with obesity. Scientific Reports, 10(1), 1291. https://doi.org/10.1038/s41598-020-58129-w [Crossref] [Google Scholar] [PubMed] [Publisher]

Desai, V., Kozyrskyj, A. L., Lau, S., Sanni, O., Dennett, L., Walter, J., & Ospina, M. B. (2021). Effectiveness of probiotic, prebiotic, and synbiotic supplementation to improve perinatal mental health in mothers: A systematic review and meta-analysis. Frontiers in Psychiatry, 12, 622181. https://doi.org/10.3389/fpsyt.2021.622181 [Crossref] [Google Scholar] [PubMed] [Publisher]

El Dib, R., Periyasamy, A. G., de Barros, J. L., França, C. G., Senefonte, F. L., Vesentini, G., Alves, M. G. O., Rodrigues, J. V. da S., Gomaa, H., Gomes Júnior, J. R., Costa, L. F., Von Ancken, T. de S., Toneli, C., Suzumura, E. A., Kawakami, C. P., Faustino, E. G., Jorge, E. C., Almeida, J. D., & Kapoor, A. (2021). Probiotics for the treatment of depression and anxiety: A systematic review and meta-analysis of randomized controlled trials. Clinical Nutrition ESPEN, 45, 75–90. https://doi.org/10.1016/j.clnesp.2021.07.027 [Crossref] [Google Scholar] [PubMed] [Publisher]

Generoso, J. S., Giridharan, V. V., Lee, J., Macedo, D., & Barichello, T. (2021). The role of the microbiota-gut-brain axis in neuropsychiatric disorders. Revista Brasileira de Psiquiatria (Sao Paulo, Brazil: 1999), 43(3), 293–305. https://doi.org/10.1590/1516-4446-2020-0987 [Crossref] [Google Scholar] [PubMed] [Publisher]

Glavanou E., & Kokorogiannis V. (2022). Advantages and Disadvantages of Probiotics and Prebiotics in the Human Body MAINWORK, University of West Attica. University of West Attica.

Gou, H.-Z., Zhang, Y.-L., Ren, L.-F., Li, Z.-J., & Zhang, L. (2022). How do intestinal probiotics restore the intestinal barrier? Frontiers in Microbiology, 13, 929346. https://doi.org/10.3389/fmicb.2022.929346 [Crossref] [Google Scholar] [PubMed] [Publisher]

Halemani, K., Shetty, A. P., Thimmappa, L., Issac, A., Dhiraaj, S., Radha, K., Mishra, P., & Mathias, E. G. (2023). Impact of probiotic on anxiety and depression symptoms in pregnant and lactating women and microbiota of infants: A systematic review and meta-analysis. Journal of Global Health, 13, 04038. https://doi.org/10.7189/jogh.13.04038 [Crossref] [Google Scholar] [PubMed] [Publisher]

Hemarajata, P., & Versalovic, J. (2013). Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. Therapeutic Advances in Gastroenterology, 6(1), 39–51. https://doi.org/10.1177/1756283X12459294 [Crossref] [Google Scholar] [PubMed] [Publisher]

Hidaka, B. H. (2012). Depression as a disease of modernity: explanations for increasing prevalence. Journal of Affective Disorders, 140(3), 205–214. https://doi.org/10.1016/j.jad.2011.12.036 [Crossref] [Google Scholar] [PubMed] [Publisher]

Ho, Y.-T., Tsai, Y.-C., Kuo, T. B. J., & Yang, C. C. H. (2021). Effects of Lactobacillus plantarum PS128 on depressive symptoms and sleep quality in self-reported insomniacs: A randomized, double-blind, placebo-controlled pilot trial. *Nutrients*, *13*(8), 2820. https://doi.org/10.3390/nu13082820 [Crossref] [Google Scholar] [PubMed] [Publisher]

Huang, R., Wang, K., & Hu, J. (2016). Effect of probiotics on depression: A systematic review and meta-analysis of randomized controlled trials. *Nutrients*, *8*(8), 483. https://doi.org/10.3390/nu8080483 [Crossref] [Google Scholar] [PubMed] [Publisher]

Jadad, A. R., Moore, R. A., Carroll, D., Jenkinson, C., Reynolds, D. J., Gavaghan, D. J., & McQuay, H. J. (1996). Assessing the quality of reports of randomized

clinical trials: is blinding necessary? *Controlled Clinical Trials*, *17*(1), 1–12. https://doi.org/10.1016/0197-2456(95)00134-4 [Crossref] [Google Scholar] [PubMed] [Publisher]

Kazemi, A., Noorbala, A. A., Azam, K., Eskandari, M. H., & Djafarian, K. (2019). Effect of probiotic and prebiotic vs placebo on psychological outcomes in patients with major depressive disorder: A randomized clinical trial. *Clinical Nutrition (Edinburgh, Scotland)*, *38*(2), 522–528. https://doi.org/10.1016/j.clnu.2018.04.010 [Crossref] [Google Scholar] [PubMed] [Publisher]

Kim, C.-S., Cha, L., Sim, M., Jung, S., Chun, W. Y., Baik, H. W., & Shin, D.-M. (2021). Probiotic supplementation improves cognitive function and mood with changes in gut Microbiota in community-dwelling older adults: A randomized, double-blind, placebo-controlled, multicenter trial. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *76*(1), 32–40. https://doi.org/10.1093/gerona/glaa090 [Crossref] [Google Scholar] [PubMed] [Publisher]

Le Morvan de Sequeira, C., Hengstberger, C., Enck, P., & Mack, I. (2022). Effect of probiotics on psychiatric symptoms and central nervous system functions in human health and disease: A systematic review and meta-analysis. *Nutrients*, *14*(3), 621. https://doi.org/10.3390/nu14030621 [Crossref] [Google Scholar] [PubMed] [Publisher]

Liu, R. T., Walsh, R. F. L., & Sheehan, A. E. (2019). Prebiotics and probiotics for depression and anxiety: A systematic review and meta-analysis of controlled clinical trials. *Neuroscience and Biobehavioral Reviews*, *102*, 13–23. https://doi.org/10.1016/j.neubiorev.2019.03.023 [Crossref] [Google Scholar] [PubMed] [Publisher]

Liwinski, T., Lang, U. E., Brühl, A. B., & Schneider, E. (2023). Exploring the therapeutic potential of gamma-aminobutyric acid in stress and depressive disorders through the gut-brain axis. *Biomedicines*, *11*(12). https://doi.org/10.3390/biomedicines11123128 [Crossref] [Google Scholar] [PubMed] [Publisher]

Luscher, B., & Fuchs, T. (2015). GABAergic control of depression-related brain states. *Advances in Pharmacology (San Diego, Calif.)*, *73*, 97–144. https://doi.org/10.1016/bs.apha.2014.11.003 [Crossref] [Google Scholar] [PubMed] [Publisher]

Majeed, M., Nagabhushanam, K., Arumugam, S., Majeed, S., & Ali, F. (2018). Bacillus coagulans MTCC 5856 for the management of major depression with irritable bowel syndrome: a randomised, double-blind, placebo controlled, multi-centre, pilot clinical study. *Food & Nutrition Research*, *62*(0). https://doi.org/10.29219/fnr.v62.1218 [Crossref] [Google Scholar] [PubMed] [Publisher]

Minayo, M. de S., Miranda, I., & Telhado, R. S. (2021). Revisão sistemática sobre os efeitos dos probióticos na depressão e ansiedade: terapêutica alternativa? *Ciencia & saude coletiva*, *26*(9), 4087–4099. https://doi.org/10.1590/1413-81232021269.21342020 [Crossref] [Google Scholar] [PubMed] [Publisher]

Mörkl, S., Butler, M. I., Holl, A., Cryan, J. F., & Dinan, T. G. (2020). Probiotics and the Microbiota-gut-brain axis: Focus on psychiatry. *Current Nutrition Reports*, *9*(3), 171–182. https://doi.org/10.1007/s13668-020-00313-5 [Crossref] [Google Scholar] [PubMed] [Publisher]

NIH. (2022). *Probiotics - Health Professional Fact Sheet*. https://ods.od.nih.gov/factsheets/Probiotics-HealthProfessional/

Pinto-Sanchez, M. I., Hall, G. B., Ghajar, K., Nardelli, A., Bolino, C., Lau, J. T., Martin, F.-P., Cominetti, O., Welsh, C., Rieder, A., Traynor, J., Gregory, C., De Palma, G., Pigrau, M., Ford, A. C., Macri, J., Berger, B., Bergonzelli, G., Surette, M. G., … Bercik, P. (2017). Probiotic Bifidobacterium longum NCC3001 reduces depression scores and alters brain activity: A pilot study in patients with irritable bowel syndrome. *Gastroenterology*, *153*(2), 448-459.e8. https://doi.org/10.1053/j.gastro.2017.05.003 [Crossref] [Google Scholar] [PubMed] [Publisher]

Pirbaglou, M., Katz, J., de Souza, R. J., Stearns, J. C., Motamed, M., & Ritvo, P. (2016). Probiotic supplementation can positively affect anxiety and depressive symptoms: a systematic review of randomized controlled trials. *Nutrition Research (New York, N.Y.)*, *36*(9), 889–898. https://doi.org/10.1016/j.nutres.2016.06.009 [Crossref] [Google Scholar] [PubMed] [Publisher]

Reiter, A., Bengesser, S. A., Hauschild, A.-C., Birkl-Töglhofer, A.-M., Fellendorf, F. T., Platzer, M., Färber, T., Seidl, M., Mendel, L.-M., Unterweger, R., Lenger, M., Mörkl, S., Dalkner, N., Birner, A., Queissner, R., Hamm, C., Maget, A., Pilz, R., Kohlhammer-Dohr, A., … Reininghaus, E. (2020). Interleukin-6 gene expression changes after a 4-week intake of a multispecies probiotic

in major depressive disorder-preliminary results of the PROVIT study. *Nutrients*, *12*(9), 2575. https://doi.org/10.3390/nu12092575 [Crossref] [Google Scholar] [PubMed] [Publisher]

Rivera, C. A., & Lennon-Duménil, A.-M. (2023). Gut immune cells and intestinal niche imprinting. *Seminars in Cell & Developmental Biology*, *150–151*, 50–57. https://doi.org/10.1016/j.semcdb.2023.01.006 [Crossref] [Google Scholar] [PubMed] [Publisher]

Romijn, A. R., Rucklidge, J. J., Kuijer, R. G., & Frampton, C. (2017). A double-blind, randomized, placebo-controlled trial of Lactobacillus helveticus and Bifidobacterium longum for the symptoms of depression. *The Australian and New Zealand Journal of Psychiatry*, *51*(8), 810–821. https://doi.org/10.1177/0004867416686694 [Crossref] [Google Scholar] [PubMed] [Publisher]

Rudzki, L., Ostrowska, L., Pawlak, D., Małus, A., Pawlak, K., Waszkiewicz, N., & Szulc, A. (2019). Probiotic Lactobacillus Plantarum 299v decreases kynurenine concentration and improves cognitive functions in patients with major depression: A double-blind, randomized, placebo controlled study. *Psychoneuroendocrinology*, *100*, 213–222. https://doi.org/10.1016/j.psyneuen.2018.10.010 [Crossref] [Google Scholar] [PubMed] [Publisher]

Sanada, K., Nakajima, S., Kurokawa, S., Barceló-Soler, A., Ikuse, D., Hirata, A., Yoshizawa, A., Tomizawa, Y., Salas-Valero, M., Noda, Y., Mimura, M., Iwanami, A., & Kishimoto, T. (2020). Gut microbiota and major depressive disorder: A systematic review and meta-analysis. *Journal of Affective Disorders*, *266*, 1–13. https://doi.org/10.1016/j.jad.2020.01.102 [Crossref] [Google Scholar] [PubMed] [Publisher]

Sánchez, B., Delgado, S., Blanco-Míguez, A., Lourenço, A., Gueimonde, M., & Margolles, A. (2017). Probiotics, gut microbiota, and their influence on host health and disease. *Molecular Nutrition & Food Research*, *61*(1). https://doi.org/10.1002/mnfr.201600240 [Crossref] [Google Scholar] [PubMed] [Publisher]

Sanchez-Villegas, A., & Martínez-González, M. A. (2013). Diet, a new target to prevent depression? *BMC Medicine*, *11*(1), 3. https://doi.org/10.1186/1741-7015-11-3 [Crossref] [Google Scholar] [PubMed] [Publisher]

Sarkar, A., Harty, S., Lehto, S. M., Moeller, A. H., Dinan, T. G., Dunbar, R. I. M., Cryan, J. F., & Burnet, P. W. J. (2018). The microbiome in psychology and cognitive neuroscience. *Trends in Cognitive Sciences*, *22*(7), 611–636. https://doi.org/10.1016/j.tics.2018.04.006 [Crossref] [Google Scholar] [PubMed] [Publisher]

Schaub, A.-C., Schneider, E., Vazquez-Castellanos, J. F., Schweinfurth, N., Kettelhack, C., Doll, J. P. K., Yamanbaeva, G., Mählmann, L., Brand, S., Beglinger, C., Borgwardt, S., Raes, J., Schmidt, A., & Lang, U. E. (2022). Clinical, gut microbial and neural effects of a probiotic add-on therapy in depressed patients: a randomized controlled trial. *Translational Psychiatry*, *12*(1), 227. https://doi.org/10.1038/s41398-022-01977-z [Crossref] [Google Scholar] [PubMed] [Publisher]

Shafie, M., Homayouni Rad, A., Mohammad-Alizadeh-Charandabi, S., & Mirghafourvand, M. (2022). The effect of probiotics on mood and sleep quality in postmenopausal women: A triple-blind randomized controlled trial. *Clinical Nutrition ESPEN*, *50*, 15–23. https://doi.org/10.1016/j.clnesp.2022.06.005 [Crossref] [Google Scholar] [PubMed] [Publisher]

Sikorska, M., Antosik-Wójcińska, A. Z., & Dominiak, M. (2023). Probiotics as a tool for regulating molecular mechanisms in depression: A systematic review and meta-analysis of randomized clinical trials. *International Journal of Molecular Sciences*, *24*(4). https://doi.org/10.3390/ijms24043081 [Crossref] [Google Scholar] [PubMed] [Publisher]

Slykerman, R. F., Hood, F., Wickens, K., Thompson, J. M. D., Barthow, C., Murphy, R., Kang, J., Rowden, J., Stone, P., Crane, J., Stanley, T., Abels, P., Purdie, G., Maude, R., & Mitchell, E. A. (2017). Effect of Lactobacillus rhamnosus HN001 in pregnancy on postpartum symptoms of depression and anxiety: A randomised double-blind placebo-controlled trial. *EBioMedicine*, *24*, 159–165. https://doi.org/10.1016/j.ebiom.2017.09.013 [Crossref] [Google Scholar] [PubMed] [Publisher]

Tian, P., Chen, Y., Zhu, H., Wang, L., Qian, X., Zou, R., Zhao, J., Zhang, H., Qian, L., Wang, Q., Wang, G., & Chen, W. (2022). Bifidobacterium breve CCFM1025 attenuates major depression disorder via regulating gut microbiome and tryptophan metabolism: A randomized clinical trial. *Brain, Behavior, and Immunity*, *100*, 233–241. https://doi.org/10.1016/j.bbi.2021.11.023 [Crossref] [Google Scholar] [PubMed] [Publisher]

Tillisch, K., Labus, J., Kilpatrick, L., Jiang, Z., Stains, J., Ebrat, B., Guyonnet, D., Legrain-Raspaud, S., Trotin, B.,

Naliboff, B., & Mayer, E. A. (2013). Consumption of fermented milk product with probiotic modulates brain activity. *Gastroenterology*, *144*(7), 1394–1401, 1401.e1-4. https://doi.org/10.1053/j.gastro.2013.02.043 [Crossref] [Google Scholar] [PubMed] [Publisher]

Wallace, C. J. K., & Milev, R. (2017). The effects of probiotics on depressive symptoms in humans: a systematic review. *Annals of General Psychiatry*, *16*(1), 14. https://doi.org/10.1186/s12991-017-0138-2 [Crossref] [Google Scholar] [PubMed] [Publisher]

World Health Organization. (2022). *Mental disorders*. https://www.who.int/news-room/fact-sheets/detail/mental-disorders [Publisher]

Zhang, X., Chen, S., Zhang, M., Ren, F., Ren, Y., Li, Y., Liu, N., Zhang, Y., Zhang, Q., & Wang, R. (2021). Effects of fermented milk containing Lacticaseibacillus paracasei strain Shirota on constipation in patients with depression: A randomized, double-blind, placebo-controlled trial. *Nutrients*, *13*(7), 2238. https://doi.org/10.3390/nu13072238 [Crossref] [Google Scholar] [PubMed] [Publisher]