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The Therapeutic Potential of Probiotics in Modulating Depressive Symptoms

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Abstract

Introduction

Major Depressive Disorder (MDD) is a complex and chronic mental health disorder that significantly affects individuals' quality of life. Recent research shows that there is a significant link between the gut microbiota and the regulation of mood, suggesting that the gut-brain axis may play a crucial role in the development and progression of MDD. The composition of gut microbiota has been found to differ between individuals with depression and healthy controls, leading to growing interest in how the gut-brain axis might influence mental health. The gut microbiota has proven that it can influence inflammatory responses, immune system regulation, and neurotransmitter production, all of which are associated with depression. Probiotics have gained attention as potential adjunctive therapy for depression because of their ability to alter the composition of the gut microbiota, regulate neurotransmitters, and reduce inflammation. Even though human studies have shown encouraging results, more research is necessary to better understand the effectiveness and therapeutic use of this intervention as the precise mechanisms are still unclear.

Objective

The purpose of this Systematic review is to explore whether probiotic supplements can be used as a treatment for depression and their therapeutic potential in modulating depressive symptoms in individuals with MDD.

Methods

A systematic search was done following PRISMA guidelines, including randomized controlled trials (RCTs) that examined the effects of probiotics supplementation in adults diagnosed with MDD.

Results:

A total of 10 RCTs met the inclusion criteria, findings were mostly positive, with 9 studies reporting significant reductions in HAM-D, MADRS, or BDI scores following probiotic supplementation. Mechanistic analyses suggested potential serotonin modulation, reduction in inflammatory markers (IL-6, TNF-α), and alterations in gut microbiota composition. However, one study found no significant difference between probiotic and placebo groups,

suggesting that probiotic efficacy may depend on strain selection, dosages, and intervention duration.

Conclusion

While probiotics show promise in reducing depression symptoms, inconsistencies across studies limit clear results. Larger, well-designed research is clearly needed to establish ideal probiotic formulations, dosages, and treatment duration. Until then, probiotics may be a helpful addition rather than the primary treatment for MDD.

Keywords:

Depression, Gut-brain axis, Gut microbiota, Probiotics, Mental health, inflammation, Psychobiotics

1. Introduction

Major Depressive Disorder (MDD) is one of the most common mental health disorders and is the leading cause of disability worldwide. According to the World Health Organization (WHO), around 280 million people in the world have depression. MDD is a complex psychiatric disorder defined by a range of different physical and psychological symptoms, such as loss of interest or pleasure, and a persistent feeling of sadness. It is a disease that affects all aspects of life, including productivity and social relationships, and has a significant burden on families, communities, and healthcare systems. Treatment methods are also very costly, both directly and indirectly, including lost wages and reduced productivity. Additionally, depression has significant social consequences, often resulting in relationship problems, social isolation, and elevated risk of substance abuse. It is also one of the leading causes of suicide. While current treatment options like antidepressants and psychotherapy are the main treatment options and may offer relief for many people, they can also be hard to access for others, and in parts of the world depression remains undiagnosed or untreated. This opens the door for researchers and scientists to explore other treatment options that can be used as a standalone or adjunctive therapy for MDD.

1.1 The Gut-Brain Axis

The connection between the gut and the brain has recently attracted researchers as a possible way to manage MDD and other mental health disorders, and there is now a significant interest in this area. The gut-brain axis (GBA) is defined as a two-way communication network that connects the central nervous system (brain) and the gastrointestinal tract (gut) through complex mechanisms and pathways.

The neural system in one of the main pathways of the GBA. The gut and the brain communicate mostly through the vagus nerve, which sends sensory data such as signals about nutrient levels and the presence of pathogens to the brain. The brain then transmits signals from the vagus nerve to regulate immune function, secretion, and gut motility. The enteric nervous system (ENS) is the brain in the gut, it's a network of neurons located in the tissues lining the esophagus, stomach, small intestine, and colon. Even though it uses the vagus nerve to send signals to the brain, it also regulates a number of digestive processes separately from the central nervous system. [1]

Another important pathway is the endocrine system. The body's reaction to stress is greatly influenced by the Hypothalamic-Pituitary-Adrenal (HPA) axis. Disruptions in HPA axis

activity can cause an increase in the release of stress hormones (e.g. cortisol), which are strongly linked to symptoms of depression. This shows that stress-related interactions between the gut and brain might play a role in mood disorders [2].

The immune system also has a key role in GBA function as most of the body's immune system is found in the gut. The gut microbiota has the ability to influence the synthesis of cytokines and other immune mediators, which can travel to the brain and influence neuroinflammation and mood regulation [1].

Finally, the GBA metabolic pathway produces neuroactive compounds, hormones, and metabolites that can cross the blood-brain barrier (BBB) and affect how the brain works. These molecules can influence the production of neurotransmitters, the flexibility of brain connections, and how we respond to stress, further linking gut-brain interactions to mental health outcomes [2].

These networks together show the great impact of the gut microbiome on brain function and behaviour. Disturbances in this sensitive balance, like an imbalance (dysbiosis) in the gut can have serious consequences on mental health, including the onset and progression of depression.

1.2 The Role of Gut Microbiota in Mental Health

The gastrointestinal tract is home to a wide range of microorganisms, mostly bacteria, that make up the gut microbiome. There are roughly 40 trillion cells of microbes that form a complex community, and it is ten times greater than the number of cells in the human body. The intestine is considered one of the most densely populated microbial habitats known on earth. A human is first exposed to microbes when they pass through the mothers' birth canal, however, new evidence suggests that babies may come in contact with some microbes while inside the womb. While all healthy humans share a 'core' of bacterial groups, each individual's gut microbiota composition is unique to them. This complex ecosystem is essential for a number of physiological functions, not just for digestion, such as nutrient absorption, immune system development, and it also influences brain function. There are many factors that affect the composition of the microbiota, such as genetics, gestational age (preterm vs. full-term birth), aging, and delivery method. However, there are some factors that are within our control, including dietary habits, medication (antibiotics, acid suppressants, and anti-diabetic drugs…), environment, lifestyle, and even weight gain.

Maintaining overall health and well-being depend on a diverse and balanced gut microbiota, and disruption and imbalances in this fragile ecosystem has been connected to a number of illnesses, including metabolic diseases, gastrointestinal disorders, and there is growing evidence that shows that the gut microbiota has a major influence in mental health as they influence processes that affect brain function and behaviour, like neurotransmitter production, modulating inflammation, and regulating stress responses [3].

Neurotransmitter production, including serotonin, dopamine, and gamma-aminobutyric acid (GABA), are directly affected by the gut microbiota. These neurotransmitters are important for mood regulation, anxiety, and cognitive function. The gut microbiota is able to produce a large amount of serotonin, commonly known as the 'happiness hormone', in the gut. Certain bacterial strains, such as *Lactobacillus* and *Bifidobacterium* are linked to increase in serotonin production by metabolizing tryptophan, an amino acid precursor to serotonin. Additionally, gut microbiota has a hand in the synthesis of dopamine (involved in motivation and reward) and gamma-aminobutyric acid (GABA), which has a calming and anti-anxiety effects). Studies suggest that disruption in the gut microbiota can reduce serotonin availability, and affect the synthesis of dopamine and GABA, which can result in depressive symptoms [4].

Increased intestinal permeability, or 'leaky gut', can result from dysbiosis that permits bacterial compounds (lipopolysaccharides LPS) to enter the circulation. Systemic inflammation and immunological responses may be triggered by this, which might lead to elevated levels of pro-inflammatory cytokines that have been linked to neuroinflammation and neurodegeneration, and chronic inflammation, and this causes a disruption of the neural signaling and increased oxidative stress in the brain. Research shows that people with major depressive disorder (MDD) often exhibit elevated levels of inflammatory markers, which indicated that there might be a strong connection between gut dysbiosis, inflammation, depression, and mental health in general [3].

The gut microbiota can also influence the body's main stress response mechanisms, the hypothalamic-pituitary-adrenal (HPA) axis. In normal settings, if the body undergoes stress, the HPA axis is activated, leading to the release of cortisol. Short-term release of cortisol is a normal adaptive response, but chronic stress can over activate the HPA axis and a release of excessive cortisol levels, which has been associated with depression. When dysbiosis occurs, it affects the regulation of the HPA axis, which leads to chronic stress and elevated levels of

stress hormones like cortisol. Chronic stress can impair brain function and has a role in the development of depression and anxiety [5].

1.3 Probiotics: Definition and Mechanism of Action

According to the World Health Organization, probiotics are live organisms that have been shown to improve host health when given in sufficient amounts [6]. These beneficial bacteria are known to boost immunological function, assist in maintaining the gut's microbial balance, and have an impact on a number of physiological functions and mood regulation. There are a number of ways in which the probiotics interact with the host, including altering the naturally present microbiota functions and it prevents pathogens from competing with it, improving the way the epithelial barrier and immune responses work, and changing the way the immune cells behave and the cytokine profiles. Recent research found a subset of probiotics known as Psychobiotics that have been specifically linked to mental health benefits, including reducing symptoms of depression and anxiety [7].

Probiotics are known to have many positive effects through multiple mechanisms, but they are especially beneficial for gut health, immune system function, and neurotransmitter synthesis. They are able to help restore the gut microbiota balance and prevent dysbiosis; disturbances in the composition of the gut microbiome (dysbiosis) have been linked to neurological disorders such as major depressive disorder (MDD). Probiotics prevent the overgrowth of pathogenic microorganisms by competing with them for nutrients and adhesion sites. This helps to maintain microbial diversity, contributing to a healthier gut environment, which is essential for overall well-being [8].

As mentioned before, a healthy gut prevents harmful substances from entering the bloodstream. However, dysbiosis can lead to increased intestinal permeability 'leaky gut', allowing bacterial metabolites (LPS) to enter the circulation, which triggers chronic inflammation and neuroinflammation. Lactobacillus and Bifidobacterium are two probiotic species that have been shown to increase the expression of tight junction proteins, which seal intestinal cells together and prevent unwanted leakage, thus strengthening the gut barrier [2]. Probiotics can also influence immune function by reducing pro-inflammatory cytokines (IL-6, TNF- α, IFN- γ), which have been associated with depression and its symptoms, and they also increase anti-inflammatory cytokines that may help counteract neuroinflammation [9].

Influencing neurotransmitter production is one of the most important ways probiotics affect mental health. Neurotransmitters are essential for mood regulation and cognitive functioning,

and they can be synthesized by specific probiotic strains. For instance, probiotics such as *Lactobacillus* and *Bifidobacterium* species are able to increase serotonin 'happiness hormone' biosynthesis through the tryptophan metabolism pathway [10]. Gamma-aminobutyric acid (GABA) is an important inhibitory neurotransmitter that reduces depression symptoms (anxiety, stress) and *Lactobacillus* species have been shown to raise GABA levels [11]. People with depression often show dysregulation in the HPA axis, which regulates the release of cortisol in response to stress. It has been found that probiotics reduce stress-induced cortisol release and regulate the HPA axis [12].

Probiotics play an important role in gut health, immune modulation, neurotransmitter production, and stress management, all of which have a direct effect on mental health. While findings suggest that probiotics may be a promising addition to the treatment of depression, more well-designed RCT's are required to fully understand their effectiveness, the most beneficial strains, and the long-term effects.

2. Purpose and Scope of Review

In recent years, probiotics' potential role in the treatment of Major Depressive Disorder (MDD) has gained more attention. Even though traditional therapies like psychotherapy and antidepressants are still the gold standard, a significant number of patients experience treatment resistance, undesirable side effects, or restricted access to these interventions. Probiotic supplementation, which may influence depression though mechanisms such as gut microbiota modulation, neurotransmitter production, immune system regulation, and HPA axis modulation, have gained interest as alternative or adjunctive treatment option. However, despite growing evidence supporting the link between the gut microbiota and mental health, the clinical efficacy of probiotics in MDD remains unclear [13].

The aim of this review is to evaluate the efficacy of probiotics in improving depressive symptoms by collecting data from randomized controlled trials involving individuals diagnosed with MDD. The review will mainly focus on the clinical outcomes of probiotic interventions in MDD, while briefly covering the mechanisms of action.

3. Research Methodology

3.1 Research Design

This study follows a systematic review approach, complying with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The main objective is to collect results from randomized controlled trials (RCTs) to assess the efficacy of probiotics in individuals with Major Depressive Disorder (MDD). PRISMA was chosen to improve transparency and accuracy in selecting studies, extracting data, and reporting, which will ensure that results can be repeated and reduce bias.

The primary focus is on clinical outcomes, such as changes in depressive symptoms measured by standardized clinical scales (e.g. HAM-D, MADRS, BDI). Mechanisms of action will be included but are not the main focus of the review. Because the included trials used different probiotic strains, dosages, and study durations, variations were qualitatively assessed to make sure that the results could be compared.

Studies will be selected based on predefined inclusion and exclusion criteria (outlined in section 2.3). Data extraction will include variables such as, (1) sample size (number of participants in treatment and control groups), (2) probiotic strain(s) used in the intervention, (3) duration of treatment, (4) Outcome measures (e.g. depression severity scales, inflammatory/bio markers…etc), and Effect size.

3.2 Search Strategy

A literature search was done across PubMed, ScienceDirect, and Google Scholar to identify relevant randomized controlled trials (RCTs) and systematic reviews. To gather all relevant studies a combination of terms and keywords was used (‘Probiotics’ or ‘Psychobiotics’ or ‘Gut Microbiota’) AND (‘Depression’ or ‘Major Depressive Disorder’ or ‘MDD’). Other variations of search terms were applied across databases to maximize results. To maintain relevance, studies published from 2010 to 2024 were included.

3.3 Selection Process

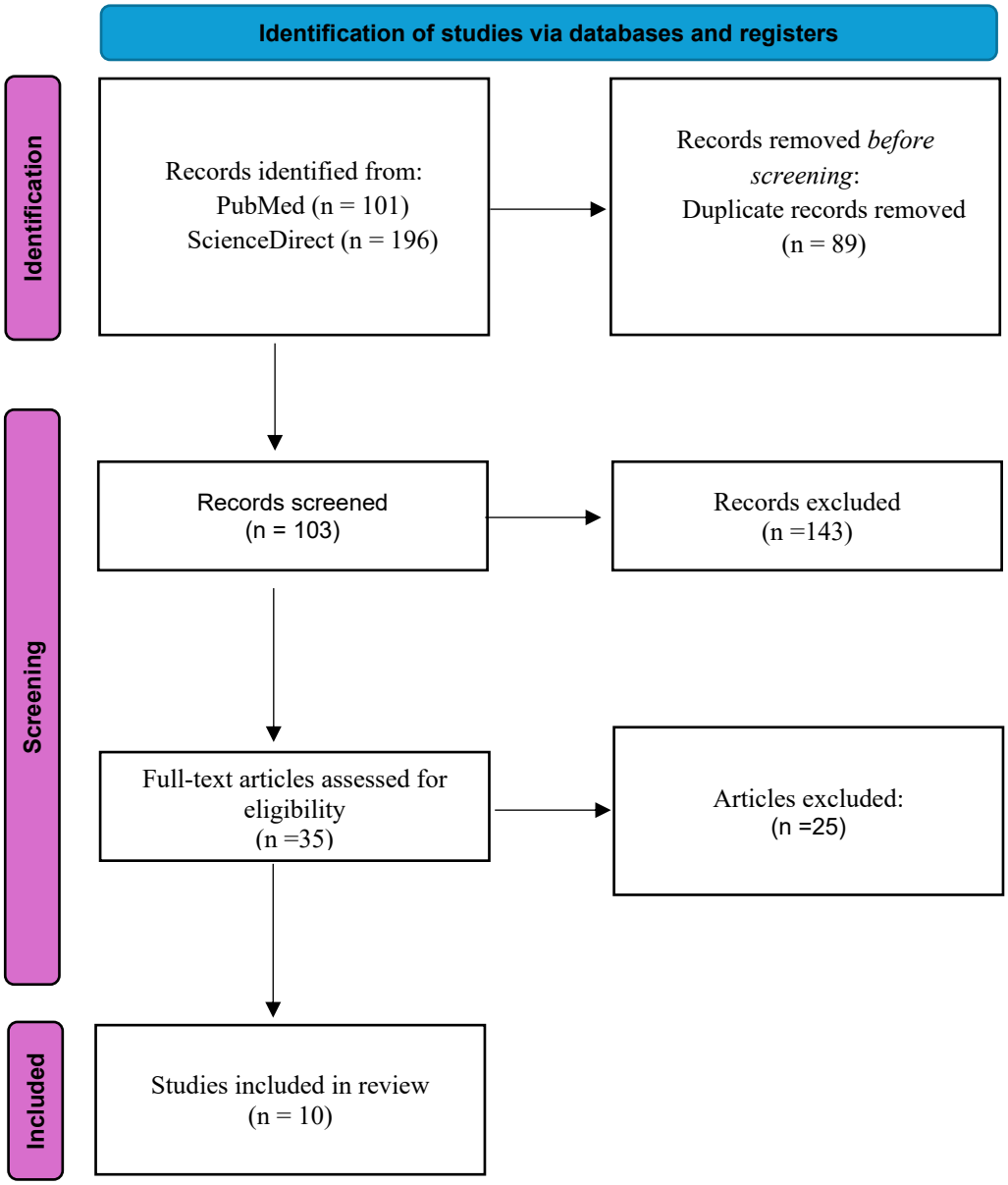

Fig 1.PRISMA graph of the selection process (source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.)

3.4 Inclusion and Exclusion Criteria

To maintain a focused analysis, this systematic review follows a predetermined inclusion and exclusion criteria based on the PICO (Population, Intervention, Comparison, Outcome) framework.

This review strictly includes human RCTs and review articles, excluding animal studies, observational studies, and research on prebiotics or symbiotic without a probiotic-only arm. The scope is limited to individuals with diagnosed MDD, meaning studies on general mood disorders, anxiety, or stress-related conditions are not considered. Studies that do not report on clinical depression outcomes were not included (e.g. those that only assess gut microbiota changes without linking them to depressive symptoms).

Population	Adults aged 18-65 years with a clinical diagnosis of Major Depressive Disorder (MDD) based on standardized diagnostic criteria.
Intervention	Probiotic supplementation administered orally, either as single-strain or multi-strain formulations. Studies investigating **probiotics alone** were prioritized, but one study that compares **probiotics, prebiotics, and placebo** was included (contains probiotic-only arm).
Comparison	Placebo-controlled RCTs were included to ensure valid comparisons.
Outcome	Depressive symptoms (BDI, HAM-D), changes in gut microbiota composition, Serotonin levels and neurotransmitter activity, inflammatory markers.

Table 1. Summary of Inclusion Criteria based on PICO

3.5 Quality Assessment

To evaluate the research quality of the included randomized controlled trials (RCTs), a quality assessment was done using the Cochrane Risk of Bias 2 (ROB 2) tool. This tool assesses the five key domains of potential bias in RCTs: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported results.

Each study was classified as having low risk, some concerns, or high risk of bias based on these five domains. Studies with appropriate randomization, blinding, and complete outcome reporting were categorized as having low risk of bias. Those with uncertainties in blinding or allocation concealment were rated as having some concerns, while studies with major issues in randomization, intervention adherence, or selective reporting were considered high risk of bias. 4 studies were classified as low-risk bias, indicating strong research design and reliability. They showed appropriate randomization, blinding, and complete outcome reporting. 5 studies were identified as having some concerns, mainly due to issues with blinding, or incomplete outcome reporting, while 1 study was found to be in high risk of bias due to and potential bias in selection reporting.

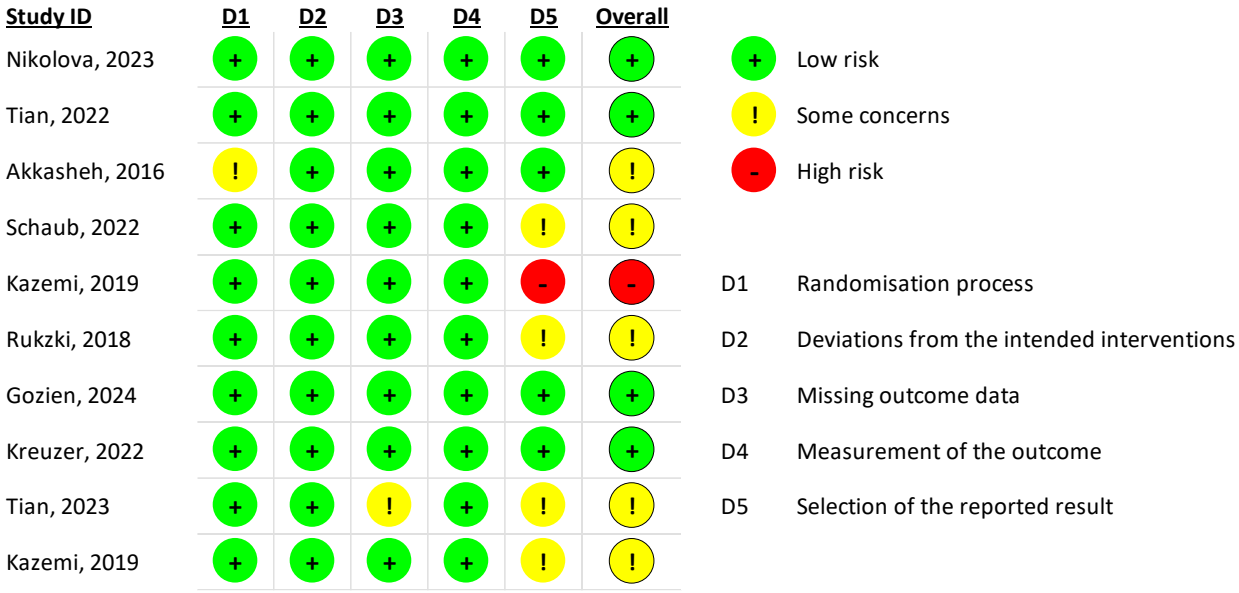

Figure 2. Quality Assessment of RCTs based on RoB 2 tool.

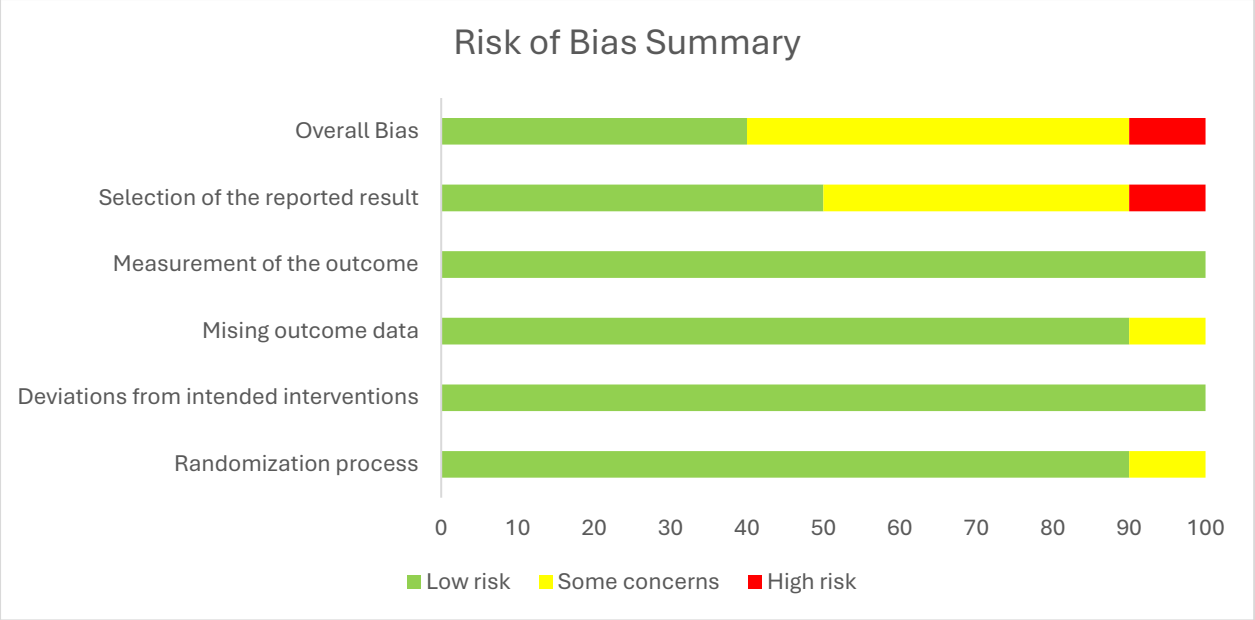

Figure 3. Risk of Bias summary (as percentage).

4. Results

4.1 Overview of Included Studies

Author & Year	Design of the study	Sample Size	Intervention:	Duration	Outcome Measures
Nikolova et al., 2023	Double-blind, placebo-controlled, pilot RCT	50 adults (80% female), diagnosed with MDD, all receiving antidepressant treatment but with incomplete response	Multistrain probiotic supplement (8 billion CFU/day) containing 14 strains of Lactobacillus, Bifidobacterium species.	8 weeks. Assessment done at baseline, week 4, and week 8.	-Primary: HAMD-17, IDS (change in depressive scores). -Secondary: HAMA, GAD-7, GGI
Tian et al., 2022	Double-blind, placebo-controlled RCT	45 adults diagnosed with MDD, with moderate-to-severe depressive symptoms.	Bifidobacterium breve CCFM1025 (10^{10} CFU/day)	4 weeks Assessment at baseline and post-intervention.	- Primary: HDRS-24, MADRS. -Secondary: BPRS, GSRS. -Biomarkers: Serum cortisol, TNF-α, IL-1β, serotonin turnover, gut microbiome composition.

Akkasheh et al., 2016	Randomized, double-blind, placebo-controlled trial.	40 adults, ages 20-55 years, diagnosed with MDD based on DSM-IV criteria.	Capsule containing Lactobacillus acidophilus (2×10^9 CFU/g), Lactobacillus casei (2×10^9 CFU/g), Bifidobacterium bifidum (2×10^9 CFU/g).	8 weeks Assessment at baseline and post-intervention	- Primary: BDI - Secondary: Metabolic markers (fasting insulin, HOMA-IR, lipid profiles) -Inflammatory markers: hs-CRP
Schaub et al., 2022	Randomized, double-blind, placebo-controlled trial.	47 adults with MDD	Multistrain probiotic supplement containing 8 different strains. 900 billion CFU/day	31 days Assessment at baseline, post-intervention, and 4 weeks after intervention	- Primary: HAM-D, BDI (German version), GSRS, STAI1. - Secondary: Gut microbe analysis (16S rRNA sequencing) -Brain activity changes (putamen activation)
Kazemi et al., 2019	Double-blind, placebo-controlled trial	110 adults (18-50 years) diagnosed with MDD, and taking anti-depressant medications	Probiotic sachets containing Lactobacillus helveticus and Bifidobacterium longum ($\geqslant 10 \times 109$ CFU)	8 weeks Assessment at baseline and post-intervention	BDI score, pro-inflammatory cytokine levels (TNF-α, IL-1β, IL-6, IL-10), urinary cortisol levels, weight and BMI.
Kazemi et al., 2019	Three-arm parallel design, placebo-controlled, double-blind, Randomized Controlled Trial	110 patients with MDD randomly assigned to 3 groups: probiotics, prebiotics, or placebo. 81 completed the trial: 28 probiotic, 27 prebiotic, and 26 placebo	Daily supplement of Lactobacillus helveticus and Bifidobacterium tongum for probiotic group.	8 weeks Assessment at baseline and post-intervention	BDI (Beck Depression Inventory), Kynurenine/Tryptophan ratio, Tryptophan/Branched-Chain Amino Acids (BCAAs) ratio.

Tian et al., 2023	Randomized, double-blind, placebo-controlled trial	30 patients with MDD, only 28 completed the study. 15 probiotic, 13 placebo	Probiotic supplement containing a mixture of *B. breve, B. longum, P. acidilactici* Each strain had a viable bacteria count of 4×10^9 CFU/g.	4 weeks. Assessments at baseline and post-intervention.	-Primary: HAMD, MADRS, GSRS. -Secondary: Serotonin modulation, gut microbiota composition, inflammation markers (CRP, TNF-α, IL-6)
Rudzki et al., 2018	Double-blind, randomized, placebo-controlled trial	78 adults diagnosed with MDD and receiving SSRIs.	Probiotic supplement of Lactobacillus plantarum 299v (10^{10} CFU/day)	8 weeks Assessment at baseline and post-intervention	-Primary: HAM-D, SCL-90, PSS-10 -Secondary: Cognitive function tests (Attention and Perceptivity tests, Stroop test, Trail making test) -Biomarkers: Kynurenine concentration, IL-6, TNF-α, IL-1β, cortisol levels.
Godzien et al., 2024	Double-blind, randomized, placebo-controlled trial	57 adults diagnosed with MDD	Lactobacillus plantarum 299v (10^{10} CFU/day)	8 weeks Assessments at baseline and post-intervention	-Primary: HAMD-17, MADRS -Secondary: Metabolomics analysis (changes in amino acids, lipid metabolism, mitochondrial function) -Biomarkers: N-acyl taurines, tryptophan metabolism,

Kreuzer et al., 2022	Randomized, double-blind, placebo-controlled trial	57 adults diagnosed with MDD	Multistrain probiotic including nine bacterial strains	4 weeks Assessments at baseline and post-intervention	-Primary: HAMD-17, MADRS -Secondary: Gut microbiota composition (16S rRNA sequencing) -Metabolomics analysis: changes in stool and serum metabolome (butyrate, amico acids, inflammatory markers)

Table 2. Summary of Included RCTs.

4.2 Key Findings and Systematic Review

4.2.1 Probiotic Strains and Their Effect on Depressive Symptoms

The included RCTs examined the efficacy of several single-strain and multi-strain probiotic supplements in reducing depressive symptoms among people with Major Depressive Disorder (MDD). Most studies measured depression severity using clinician-rated scales such as the Hamilton Depression Rating Scale (HAM-D/HAMD-17), Montgomery-Åsberg Depression Rating Scale (MADRS), and the Beck Depression Inventory (BDI). While a number of studies found that statistically probiotic supplementation improved depressive symptoms significantly, the strength of the effect differed based on the strain or strains used, dosage, and length of study.

The effects of multi-strain probiotics, which contain a combination of Lactobacillus and Bifidobacterium species, were assessed in several studies. For example, over the course of eight weeks, [14] suggest that multi-strain probiotic blend (8 billion CFU/day) may have a clinically relevant effect on depressive symptoms, with moderate effect sizes observed at both Week 4 (HAMD-17: SES = 0.70, 95% CI: 0.01–0.98) and Week 8 (IDS: SES = 0.64, 95% CI: 0.03–0.87, p = 0.04). These findings align with previous studies indicating a potential role of probiotics in improving mood disorders by modulating gut microbiota and neurotransmitter production. Similarly, [12] observed that a multi-strain probiotic formulation (900 billion CFU/day) given for 31 days shows that HAM-D scores decreased significantly in the probiotic group compared to placebo from baseline to post-intervention (week 4) ($p < 0.05$, $d = 0.62$) and from baseline to follow-up (week 8) ($p < 0.01$, $d = 0.95$), indicating a moderate to large effect size. Other studies, such as [15], showed significant

reductions in BDI scores (-5.7 ± 6.4 points vs. −1.5 ± 4.8 points in the placebo group, p = 0.001) with a combination of Lactobacillus acidophilus, L. casei, and Bifidobacterium bidifum, suggesting a clinically relevant antidepressant effect, while [16] reported a significant reduction in BDI scores with L. helveticus and B. longum (p = 0.042).

Of the single-strain probiotics examined, Lactobacillus Plantarum 299v was studied in two randomized controlled trials. [11] and [17] showed that supplementing with L. plantarum 299v for 8 weeks has no significant reductions in depressive symptoms as measured by HAM-D scores compared to placebo.

Two studies examined Bifidobacterium breve CCFM1025, another single-strain probiotic. [18] found that supplementation with B. breve (10^{10} CFU/day) for 4 weeks showed significantly greater reductions in depression severity. HAMD-24 and MADRS scores were significantly reduced in the probiotic group compared to placebo ($p < 0.05$), with a moderate effect size ($d = 0.64–0.65$), suggesting antidepressant potential. However, [9] reported higher reductions in depression severity when B. breve was combined with two additional strains (B. longum, P. acidilactici). HAM-D scores (p < 0.001, d = 0.553), MADRS scores (p = 0.003, d = 0.319), and BPRS scores (p < 0.001, d = 0.473) This suggests that multi-strain formulations may have combined benefits.

While most studies showed that probiotic supplements had beneficial effects, [19] evaluated the impact of multi-species probiotic supplement on depression outcomes but found both the probiotic and placebo groups showed improvements in HAM-D and BDI-II scores, but no statistically significant difference between groups (p = 0.162 for BDI-II, p = 0.459 for HAM-D), however, they did observe changes in the composition of the gut microbiota and stool metabolites. This suggests that while probiotics may have some beneficial effects, hey did not outperform placebo in this study.

Overall, it appears that multi-strain probiotics were more effective than single-strain formulations at lowering depressive symptoms. However, some single-strain probiotics (e.g. B. breve CCFM1025) also showed notable benefits, especially when taken for at least 8 weeks. A few trials showed no significant effect, possibly because of differences in strains, patient characteristics, or study duration, but the majority of studies found at least some improvement in depression scores. The variation in results implies that the efficacy of treatment for MDD is significantly influenced by strain selection, dosage, and treatment duration.

4.2.2 Mechanisms of Action

While most RCTs focused on clinical outcomes, several also looked at the biological mechanisms behind the effects of probiotics. The most often studied mechanisms are (1) Serotonin modulation, (2) inflammation reduction, (3) gut microbiota changes, and (4) kynurenine pathway regulation.

Serotonin plays an important role in mood regulation, and probiotic supplements may enhance serotonin turnover. [18] shows that Bifidobacterium breve CCFM678 altered gut microbiota supplementation, increasing its diversity and enhancing tryptophan metabolism. The probiotic group had higher levels of tryptophan and serotonin, as well as reduced serotonin turnover ($p = 0.029$, $d = 0.681$), suggesting more serotonin availability in the brain. According to [9] Bifidobacterium breve CCFM1025, Bifidobacterium longum CCFM687, and P. acidilactici CCFM6432 all raised serotonin levels and its availability in the brain, while also reducing its turnover. While in [20] probiotic supplementation led to a significant decrease in kynurenine/tryptophan ratio compared to placebo ($p = 0.04$), indicating a potential shift in tryptophan metabolism away from neurotoxic kynurenine pathway activation. There was also a increase in the tryptophan/isoleucine ration in the probiotic group ($p = 0.023$), suggesting enhanced tryptophan bioavailability for serotonin synthesis.

Changes in gut microbiota after probiotic supplementation were evaluated in a number of studies. [12] reported that a multi-strain probiotic mixture significantly increased Lactobacillus abundance ($p = 0.03$), correlating with improvements in HAM-D scores. Although [17] mainly concentrated on metabolomics rather than direct clinical effects, they did observe notable metabolic changes in the composition of the gut microbiota. [19] reported that probiotic interventions led to significant shifts in gut microbiota composition. It showed an increase in the levels of short-chain fatty acids (SCFAs) such as butyrate, along with higher concentrations of branched-chain amino acids (BCAAs) (valine, isoleucine, alanine, lysine), and other metabolic compounds including sarcosine and methylamine. These metabolic shifts suggest potential benefits for gut barrier function and neurotransmitter precursor availability. Additionally, increased abundance of butyrate-producing bacteria, such as Faecalibacterium and Ruminococcus species, was observed in the probiotic group, aligning with prior evidence supporting the role of SCFAs in modulating neuroinflammation and the gut-brain axis.

Chronic inflammation has been linked to MDD, with elevated IL-6, TNF-α, and CRP observed in depressed patients. In a study done by [15], the probiotic group showed significant reductions in systemic inflammation and oxidative stress markers. Notably, serum high-sensitivity C-reactive protein (hs-CRP) levels decreased significantly in the probiotic group compared to placebo ($p = 0.03$), indicating potential anti-inflammatory effects. Probiotic supplementation also led to increased plasma glutathione (GSH) levels, suggesting an improvement in antioxidant capacity ($p = 0.02$). Furthermore, insulin resistance markers improved, with a reduction in serum insulin levels ($p = 0.03$) and HOMA-IR index values ($p = 0.03$) in the probiotic group compared to placebo.

[11] the study observed a significant reduction in kynurenine (KYN) concentration in the probiotic group, suggesting a possible neuroprotective effect via modulation of the kynurenine pathway, which has been linked to depression-related cognitive dysfunction. And improved cognitive function ($p < 0.05$. These findings suggest that while LP299v may not directly alleviate depressive symptoms, it could offer cognitive benefits for MDD patients, possibly through microbiota-gut-brain interactions.

[17] noted that supplementation with Lactobacillus plantarum 299v a significant reduction in N-acyl taurines (NATs), a metabolite linked to neuroinflammatory pathways. Additionally, the probiotic group exhibited a 4.5 times greater decrease in acylcarnitine levels compared to placebo, suggesting improvements in mitochondrial energy metabolism. Elevated L-histidine and D-valine levels were also observed, which may play a role in neurotransmitter synthesis and cognitive function.

4.2.3 Clinical Outcomes: Efficacy, Safety, and Adverse Effects

Probiotic supplementation was found to be highly tolerable in most of the studies, with no severe adverse effects reported.

The majority of studies showed high adherence to probiotic supplements, with dropout rates varying between 5% and 15%. According to [14], there were no significant differences in dropout rates between the probiotic and placebo groups ($p > 0.05$).

Some studies reported mind gastrointestinal side effects, such as gas and bloating, but these did not differ significantly from placebo. The safety profile of probiotics is further supported by [12] which found that changes in gut microbiota happened without causing negative health effects.

5. Discussion

5.1 Summary of Main Findings

This systematic review assessed the efficacy of probiotic supplementation in reducing depressive symptoms among individuals diagnosed with Major Depressive Disorder (MDD). A total of 10 randomized controlled trials (RCTs) met the inclusion criteria ranging from 40 to 110 participants and intervention durations between 4 to 8 weeks. The HAM-D (Hamilton Depression Rating Scale), MADRS (Montgomery-Åsberg Depression Rating Scale), and BDI (Beck Depression Inventory) were the main tools used to measure the severity of depression.

Overall, the results indicate that probiotic supplementation may have beneficial effects on depressive symptoms, though the extent of improvement varied between studies. A number of RCTs, especially those that used multi-strain probiotic mixtures, reported statistically significant reductions in depression scores when compared to placebo with moderate to large effect sizes [12], [14]. Some studies indicated that probiotics were particularly effective for those whose antidepressant therapy did not completely alleviate their symptoms, which suggests that they may be used as an adjunctive treatment in depression.

Among the single-strain probiotics, Bifidobacterium breve CCFM1025 showed the most promising benefits on cognitive performance and depressive symptoms, with reductions in HAMD-24 and MADRS scores [18]. However, Lactobacillus plantarum 299v did not reduce depression scores in two RCTs [11], [17], but it did show cognitive benefits and metabolic changes. Furthermore, studies using probiotic mixtures with multiple strains frequently showed greater benefits than single strains, suggesting that strain synergy might improve therapeutic results.

In terms of mechanisms, probiotic supplementation appeared to influence several pathways involved in MDD, including serotonin modulation [9], [18], inflammation reduction [15], [20], gut microbiota composition [14], [19], and kynurenine pathway regulation [11]. However, not all biological changes correlated with clinical improvements, suggesting that while probiotics induce physiological changes, their antidepressant effects may depend on additional factors such as baseline gut microbiota composition and patient characteristics.

However, not every study found notable improvements. Variability in treatment response was highlighted by some trials that reported no apparent distinction between the probiotic and placebo groups. This may be related to differences in study design, strain selection, dose,

participant characteristics, and intervention duration. Shorter treatment duration studies could not have recorded long-term benefits, and differences in patient demographics (e.g. use of antidepressants or severity of depression) might have affected results.

5.2 Limitation

While this review gives insights into the potential role of probiotics in MDD, several limitations must be considered for both the included RCTs and the review process itself.

One important problem is that the small sample sizes of many of the included studies make it difficult to determine if the results apply to a larger population. Most trials also had brief intervention times -usually 4 to 8 weeks- which might not be long enough to fully benefit from probiotics in treating depression. Since MDD is a long-term condition, it's unclear if probiotics offer long-term effects or if continues use is required.

Another problem is the different types of probiotics used in various trials. The studies tested many strains, doses, and forms of probiotics, which makes it hard to compare the results or figure out which strains work best. The studies were designed in different ways, some examined probiotics used together with antidepressants, while others focused on probiotics alone as a cure. It's not clear if probiotics are most effective when used alone or along with other treatments.

Additionally, long-term follow-up was rarely done, so we can't know if the benefits from taking probiotics last after stopping them. This is important when considering probiotics as a long-term strategy for managing depression.

This review also has some limitations. Only 10 RCTs were included, which makes findings less compelling. The studies used different depression scales (HAMD-D, MADRS, BDI), making it hard to compare them directly. A meta-analysis couldn't be done because the probiotic strains, doses, and study designs varied. Instead, the results were presented in a qualitative way.

Even with these drawbacks, the data shows that probiotics could be a promising method in managing depression. However, more well-designed, longer-term studies are needed to prove their effectiveness and to determine the best strains, dosage, and treatment duration for people with MDD.

6. Conclusion and Future Directions

Overall, the findings of this review support the results of other systematic reviews and meta-analyses that investigated the role of probiotics in depression, suggesting that they may have beneficial effects, especially as a combination treatment. Further research is required and should focus on larger, longer trials with similar probiotic strains and mixtures to better understand their effects, and to determine if probiotics are more effective on their own or combined with other treatments. It is also important to understand the underlying biological mechanisms through more advanced research methods.

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