

Research Article

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Efficacy of Probiotics in Reducing Depressive Symptoms: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Dr. Prashant Mangla¹, Dr. Aarushi Mangla^{2*}

¹Associate Professor, Department of Psychiatry, Banas Medical College and Research Institute, Palanpur, Gujarat, India. Email: manglaprashant1@gmail.com

²Associate Professor, Department of Microbiology, Banas Medical College and Research Institute, Palanpur, Gujarat, India. Email: agrawalaarushi1@gmail.com

*Corresponding Author: Dr. Aarushi Mangla

Email: agrawalaarushi1@gmail.com

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Abstract: Background and objective: Despite the availability of many forms of treatment, depression continues to be a leading cause of disability and burden worldwide. Recent evidence has shown that probiotics may be a potential treatment option, indicating an important role of the gut–brain axis in depression. However, findings from randomized controlled trials (RCTs) continue to remain mixed. Our study aimed to evaluate the effectiveness of probiotics in reducing depressive symptoms through a systematic review and meta-analysis of randomized controlled trials. **Methods:** We systematically searched databases such as PubMed/MEDLINE and Google Scholar for randomized controlled trials published in the last 10 years that examined the effects of probiotics on depressive symptoms in humans. The primary outcome measured was the change in depressive symptoms at the end of treatment, using validated scales. We used a random-effects model to calculate pooled standardized mean differences (Hedges' g) with 95% confidence intervals (CI), and subgroup analyses were conducted on the basis of baseline severity of depression and duration of intervention. **Results:** 15 RCTs with a total of 1,066 participants were included in the meta-analysis. We found that probiotic supplementation was associated with a statistically significant reduction in depressive symptoms compared to placebo (Hedges' $g = -0.50$; 95% CI: -0.86 to -0.15 ; $p = 0.005$), with substantial heterogeneity among studies ($I^2 = 87\%$). Subgroup analysis showed a significant effect in moderate-to-severe depression ($g = -0.61$; 95% CI: -1.17 to -0.05 ; $p = 0.03$), but not in minimal-to-mild depression ($g = -0.37$; 95% CI: -0.79 to 0.04 ; $p = 0.08$). Also, significant effects were observed in interventions lasting ≥ 8 weeks ($g = -0.36$; 95% CI: -0.63 to -0.09 ; $p = 0.008$), but not in those < 8 weeks ($g = -0.96$; 95% CI: -2.37 to 0.45 ; $p = 0.18$). However, differences in subgroups were not found to be statistically significant. Risk of bias was observed to be generally low, and funnel plot analysis did not suggest any strong evidence of publication bias. **Conclusion:** Treatment with probiotics is associated with a moderate and statistically significant reduction in depressive symptoms and may be used as an adjunctive treatment option for the management of depression. Further trials are needed to establish the optimal formulations, dosing regimens, and long-term effects of probiotics.

Keywords: Probiotics; Depression; Depressive Symptoms; Gut–Brain Axis; Microbiome; Randomized Controlled Trials; Meta-analysis.

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INTRODUCTION

Major depressive disorder (MDD) is a leading cause of disability and a substantial burden worldwide. It affects approximately 332 million people globally across all age groups [1]. Although many pharmacological and psychological treatments are available, a large number of patients continue to experience inadequate response, relapse, or treatment-related adverse effects, which underscores the need for alternative and adjunctive treatment strategies [2, 3].

In recent years, there has been growing evidence that highlights the importance of the gut-brain axis in depression, a bidirectional network linking the central nervous system with the gastrointestinal microbiota [4]. The gut microbiome has been shown to play a crucial role in controlling neuroinflammatory processes, neurotransmitter synthesis, and stress-related pathways. All of these factors have been implicated in the pathophysiology of depression [5]. Changes in gut microbial composition, or dysbiosis, have been associated with depressive symptoms, suggesting that interventions targeting the gut microbiome may have therapeutic potential [6].

In this context, a promising intervention has emerged in the form of probiotics, which are live microorganisms that may confer health benefits when administered in adequate amounts [7]. Previous studies have shown that certain probiotic strains can influence central nervous system function through various mechanisms such as modulation of the hypothalamic-pituitary-adrenal (HPA) axis, immune signaling, and production of neuroactive metabolites such as short-chain fatty acids and neurotransmitter precursors [5, 8]. Preclinical studies have shown that probiotics can reduce anxiety- and depression-like behaviors. Also, improvements in mood and psychological well-being have been reported in clinical trials.

However, there have been inconsistent findings from randomized controlled trials (RCTs) evaluating the efficacy of probiotics in reducing depressive symptoms due to variability in study design, probiotic strains, duration of treatment and outcome measures. Also, factors such as baseline severity of depression and duration of intervention which may influence treatment efficacy, have not been consistently measured in previous studies. Past systematic reviews have pointed to possible benefits of probiotics in lowering depressive symptoms, but the conclusions are limited due to differences in methods and a lack of in-depth subgroup analyses [9].

Thus, our systematic review and meta-analysis aim to evaluate the effectiveness of probiotic interventions in reducing depressive symptoms across RCTs. Furthermore, subgroup analyses were done to assess whether treatment effects vary according to baseline severity of depression (minimal to mild vs moderate to severe) and duration of intervention (<8 weeks vs ≥ 8 weeks). By combining the available evidence, this study seeks to clarify whether probiotics could serve as a possible therapeutic option for depression.

METHODS

Study Design and Reporting Guidelines

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the review methodology was predefined prior to data extraction and analysis.

Search Strategy

We performed a comprehensive literature search in PubMed/MEDLINE and Google Scholar from database inception to 19th of April 2026. The search strategy combined MeSH terms and free-text terms related to probiotics and depression. Keywords included “probiotics”, “microbiome” and “psychobiotics” combined with “depression”, “major depressive disorder”, “depressive symptoms” and “mood disorder”, using Boolean operators (AND, OR).

Filters were applied to identify randomized controlled trials involving human participants and publications from last 10 years. Reference lists of included studies and relevant reviews were manually screened to identify additional eligible studies.

Eligibility Criteria

Inclusion criteria for studies included: (1) randomized controlled trials; (2) involved human participants with depressive symptoms or diagnosed with depressive disorders; (3) evaluated probiotic interventions compared with placebo or control; and (4) reported quantitative outcomes using validated depression rating scales.

Studies that were excluded from this review were observational studies, reviews, animal studies, conference abstracts without full text, or those that did not report sufficient data for effect size calculation.

Study Selection

After searching the database, all the identified records were imported into a reference management



software and duplicates were removed. Titles and abstracts of identified records were screened independently by both authors for eligibility. This was followed by a full-text assessment of potentially relevant studies. Discrepancies between the authors were resolved through discussion.

Data Extraction

Data was independently extracted by both authors independently using a standardized data extraction sheet in excel. This included the study characteristics (author, year, country), characteristics of study participants, sample sizes of both intervention and control groups, details of intervention, duration of treatment, outcome measures used and results. For continuous outcomes, mean and standard deviation values were extracted for both intervention and control groups at the end of treatment. The most commonly used validated scale was selected when multiple depression scales were reported in a study.

Outcome Measures

The primary outcome which was measured was the change in depressive symptoms using validated rating scales at the end of the intervention period. When outcome scales were reported at multiple time points, data at the end of treatment was used for analysis.

Risk of Bias Assessment

The risk of bias of included studies was assessed independently by both authors using the Cochrane Risk of Bias (RoB) tool under the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Each study was classified as having low risk of bias, unclear risk of bias, or high risk of bias.

Data Synthesis and Statistical Analysis

Data was entered in RevMan 5.4 software and meta-analysis was conducted using a random-effects model to account for the potential heterogeneity present across studies. As different depression scales were used across studies, effect sizes for continuous outcomes were calculated as standardized mean differences (Hedges' g) with 95% confidence intervals. I^2 statistic was used to assess statistical heterogeneity, with values of 25%, 50%, and 75% representing low, moderate and high heterogeneity, respectively.

Subgroup Analysis

We conducted subgroup analyses based on baseline severity of depression (minimal to mild vs moderate to severe) and duration of intervention (<8 weeks vs ≥ 8 weeks). Chi-square test was used to assess the differences between subgroups.

Publication Bias

Publication bias was assessed through visual inspection of the funnel plot. Due to methodological constraints, a formal statistical test for funnel plot asymmetry was not performed.

Ethical Considerations

As this study is a systematic review and meta-analysis of previously published randomized controlled trials and does not involve direct interaction with human participants or collection of primary data, ethical approval and informed consent were not required. All included studies reported that they had obtained appropriate ethical approvals and were conducted in accordance with the ethical standards.

RESULTS

Study Selection

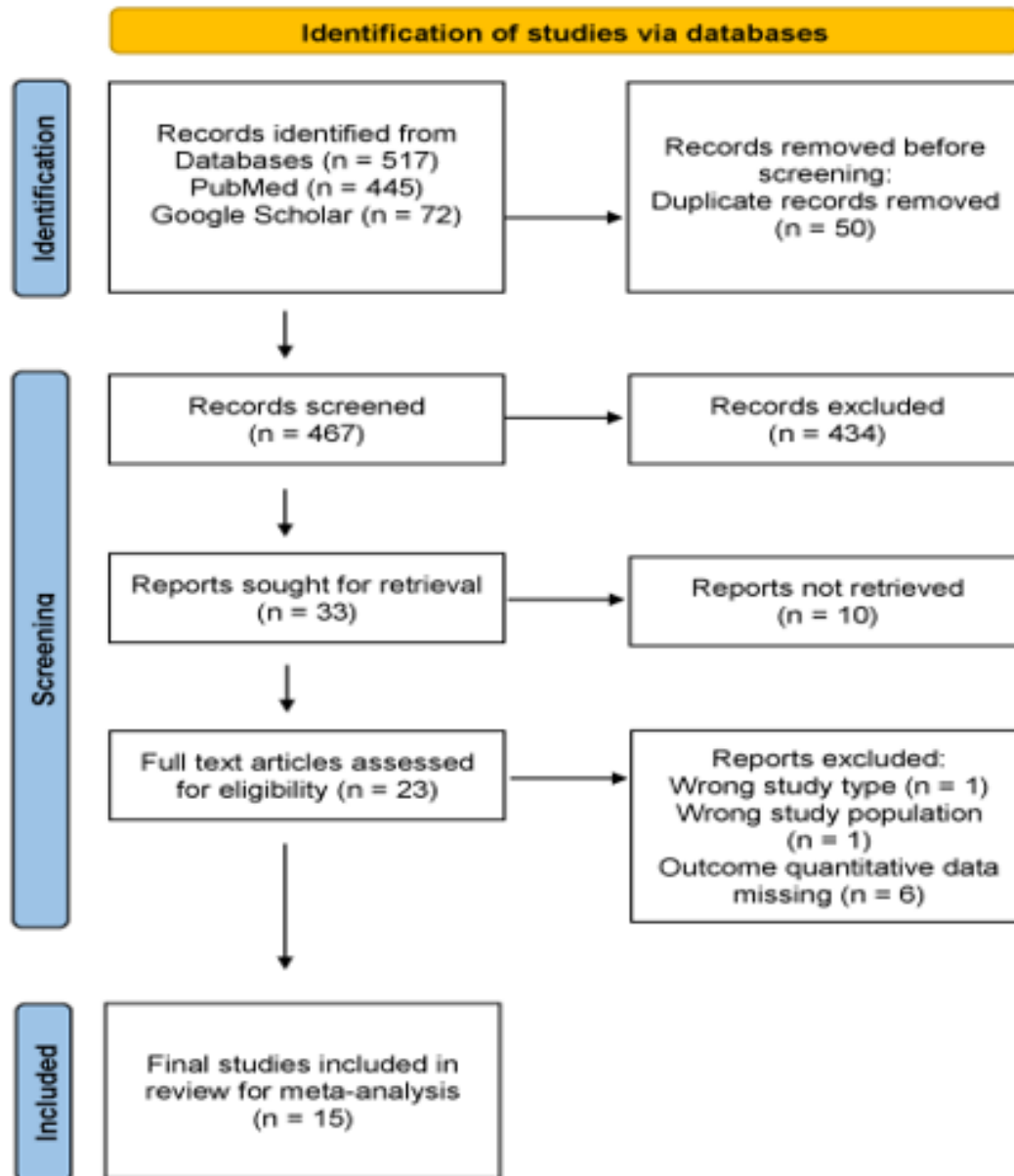


Figure 1. PRISMA flow diagram of the study selection process

After database searching, we identified a total of 517 records which included 445 records from PubMed/MEDLINE and 72 records from Google Scholar. 50 duplicate records were removed and 467 remaining records remained were screened. 434 records were excluded after title and abstract screening, and 33 reports were sought for full-text retrieval. Out of these, we could not retrieve full texts of 10 reports which were then excluded. Out of the

remaining total of 23 full-text articles which were assessed for eligibility, 8 were excluded for the following reasons: wrong study design ($n = 1$), inappropriate study population ($n = 1$), and insufficient quantitative outcome data ($n = 6$).

In the end, 15 randomized controlled trials met the inclusion criteria and were included in our systematic review and meta-analysis.

Study Characteristics**Table 1. Study Characteristics**

Study ID	Author	Year	Country	Population	Sample Size Total	Intervention n	Control n	Study Design	Duration	Mean Age (SD)	Gender (% female)
S1	Pinto-Sanchez <i>et al.</i> [10]	2017	Canada	IBS + Depression	44	22	22	RCT DBPC	6 weeks	-	54.5
S2	Romijn <i>et al.</i> [11]	2017	New Zealand	Depression	79	40	39	RCT DBPC	8 weeks	-	78.5
S3	Kazemi <i>et al.</i> [17]	2018	Iran	Depression	74	38	36	RCT DBPC	8 weeks	-	68.9
S4	Majeed <i>et al.</i> [18]	2018	India	IBS + Depression	40	20	20	RCT DBPC	90 days	-	85
S5	Chahwan <i>et al.</i> [19]	2019	Australia	Depression	71	34	37	RCT TBPC	8 weeks	-	69
S6	Reininghaus <i>et al.</i> [20]	2020	Austria	Depression	82	42	40	RCT DBPC	4 weeks	-	78
S7	Haghighat <i>et al.</i> [21]	2021	Iran	CKD + Depression	50	25	25	RCT DBPC	12 weeks	-	-
S8	Lee <i>et al.</i> [22]	2021	Korea	Subclinical depression	156	78	78	RCT DBPC	8 weeks	38.26 (10.94)	68
S9	Zhang <i>et al.</i> [23]	2021	China	Depression + Constipation	82	41	41	RCT DBPC	9 weeks	-	63.8
S10	Baião <i>et al.</i> [24]	2022	UK	Depression	71	35	36	RCT DBPC	4 weeks	28.8 (8.93)	63.4
S11	Nikolova <i>et al.</i> [12]	2023	UK	Depression	49	24	25	RCT DBPC	8 weeks	31.7 (9.8)	80
S12	Moschonis <i>et al.</i> [13]	2024	Australia	Subclinical depression	39	19	20	RCT DBPC	12 weeks	-	66.7
S13	Ahmad <i>et al.</i> [14]	2025	India	Depression	99	50	49	RCT DBPC	12 weeks	34.7 (9.2)	51
S14	Mosavat <i>et al.</i> [15]	2026	Iran	Substance induced depression	50	25	25	RCT DBPC	4 weeks	-	-
S15	Sadeghi <i>et al.</i> [16]	2026	Iran	Smokers + Depression	80	40	40	RCT DBPC	12 weeks	-	21.6



In our meta-analysis, a total of 15 randomized controlled trials (RCTs) involving 1,066 participants were included [10-24]. Sample sizes of study participants ranged from 39 to 156 per study. The studies were conducted across multiple countries, including Iran (n = 4), the United Kingdom (n = 2), Australia (n = 2), India (n = 2), and one study each from Canada, New Zealand, Austria, Korea, and China. All of the studies were of double-blind placebo-controlled design, except one study which was a triple-blind placebo-controlled design.

Participants included in the studies were individuals who were clinically diagnosed with depression or with subclinical depressive symptoms. Some studies included populations with comorbid conditions such as irritable bowel syndrome (IBS), chronic kidney

disease (CKD), constipation, substance-induced depression, and smoking. In studies where reported, the mean age of participants ranged from 28.8 to 38.3 years and the proportion of female participants ranged from 21.6% to 85%.

The duration of probiotic interventions in the included studies ranged from 4 weeks to 12 weeks. Out of the fifteen studies, four studies were categorized as short-duration interventions (<8 weeks), while eleven studies had longer durations (≥8 weeks).

Overall, we found that there was variability in participant characteristics and clinical populations, which indicated clinical heterogeneity.

Intervention Characteristics**Table 2. Intervention Characteristics**

Study ID	Type	Strains	Dose (CFU)	Formulation	Frequency	Comparator	Adherence (%)
S1	Probiotic	B. longum NCC3001	10×10^9	Sachet	1/day	Placebo	86.4
S2	Probiotic	L. helveticus R0052 + B. longum R0175	$\geq 3 \times 10^9$	Sachet	1/day	Placebo	87.4
S3	Probiotic	L. helveticus R0052 and B. longum R0175	$> 10 \times 10^9$	Sachet	1/day	Placebo	91.9
S4	Probiotic	B. coagulans MTCC 5856	2×10^9	Tablet	1/day	Placebo	66.7
S5	Probiotic	Bifidobacterium bifidum W23, Bifidobacterium lactis W51, Bifidobacterium lactis W52, L. acidophilus W37, Lactobacillus brevis W63, Lactobacillus casei W56, Lactobacillus salivarius W24, Lactococcus lactis W19 and Lactococcus lactis W58	2.5×10^9	Sachet	2/day	Placebo	66.2
S6	Probiotic	B. bifidum W23, B. lactis W51, B. lactis W52, L. acidophilus W22, L. casei W56, L. paracasei W20, L. plantarum W62, L. salivarius W24 and L. lactis W19	7.5×10^9	Sachet	1/day	Placebo	74.4
S7	Probiotic	Lactobacillus acidophilus strain T16, Bifidobacterium bifidum strain BIA-6, Bifidobacterium lactis strain BIA-7, Bifidobacterium longum strain BIA-8	2.7×10^7	Capsule	4/day	Placebo	84
S8	Probiotic	Lactobacillus reuteri NK33 and Bifidobacterium adolescentis NK98	2.5×10^9	Capsule	2/day	Placebo	78.2
S9	Probiotic	Lactocaseibacillus paracasei YIT 9029	1.0×10^{10}	Beverage	1/day	Placebo	84
S10	Probiotic	Bacillus subtilis PXN 21, Bifidobacterium bifidum PXN 23, Bifidobacterium breve PXN 25, Bifidobacterium infantis PXN 27, B. longum PXN 30, Lactobacillus acidophilus PXN 35, Lactobacillus delbrueckii ssp. bulgaricus PXN 39, Lactobacillus casei PXN 37, Lactobacillus plantarum PXN 47, Lactobacillus rhamnosus PXN 54, Lactobacillus helveticus PXN 45, Lactobacillus salivarius PXN 57, Lactococcus lactis ssp. lactis PXN 63, Streptococcus thermophilus PXN 66	2×10^9	Capsule	1/day	Placebo	71.8



S11	Probiotic	Bacillus subtilis, Bifidobacterium bifidum, Bifidobacterium breve, Bifidobacterium infantis, Bifidobacterium longum, Lactobacillus acidophilus, Lactobacillus delbrueckii subsp bulgaricus, Lactobacillus casei, Lactobacillus plantarum, Lactobacillus rhamnosus, Lactobacillus helveticus, Lactobacillus salivarius, Lactococcus lactis, and Streptococcus thermophilus	2×10^9	Capsule	4/day	Placebo	97.2
S12	Probiotic	Limosilactobacillus fermentum LF16 (DSM26956), Lactocaseibacillus rhamnosus LR06 (DSM21981), Lactiplantibacillus plantarum LP01 (LMG P-21021) and Bifidobacterium longum 04 (DSM23233)	1×10^9	Capsule	1/day	Placebo	76.9
S13	Probiotic	Lactobacillus rhamnosus GG and Bifidobacterium longum	1.5×10^9	Capsule	1/day	Placebo	-
S14	Probiotic	Lactobacillus helveticus and Bifidobacterium longum	3×10^9	Capsule	2/day	Placebo	80
S15	Probiotic	Lactobacillus acidophilus, Bifidobacterium longum, Bifidobacterium bifidum, and Bifidobacterium lactis	1.8×10^9	Capsule	1/day	Placebo	92.5



All the included studies evaluated the efficacy of orally administered probiotic formulations compared with placebo control groups.

The probiotic preparations used in the studies included both single-strain and multi-strain formulations. Single-strain formulations were used only in a few studies and included *Bifidobacterium longum* NCC3001 and

Lactocaseibacillus paracasei YIT 9029. However, most of the trials used multi-strain combinations of probiotics, primarily consisting of species from the genera *Lactobacillus* and *Bifidobacterium*. Some studies used complex formulations containing up to 14 different strains of probiotics.

There was substantial variation in the daily dose of probiotics across studies, ranging from 2.7×10^7 to 1.0×10^{10} colony-forming units (CFU). In most of the studies, interventions were administered once daily,

although some studies used twice a day or four times a day dosing regimen.

Different forms were used to deliver the probiotic formulations which included capsules, sachets, tablets, and beverages, with capsules and sachets being the most commonly used delivery methods. To maintain blinding, the placebo comparators were matched for appearance and administration schedule in all the studies. Adherence to the intervention was found to be generally high across studies, ranging from 66.2% to 97.2% where reported.

Overall, while all the studies evaluated the efficacy of probiotic supplementation for depressive symptoms, it was observed that there was considerable variability in strain composition, dosage, and formulation, which contributed to clinical heterogeneity.

Primary Outcome Effects of Probiotics on Depressive Symptoms

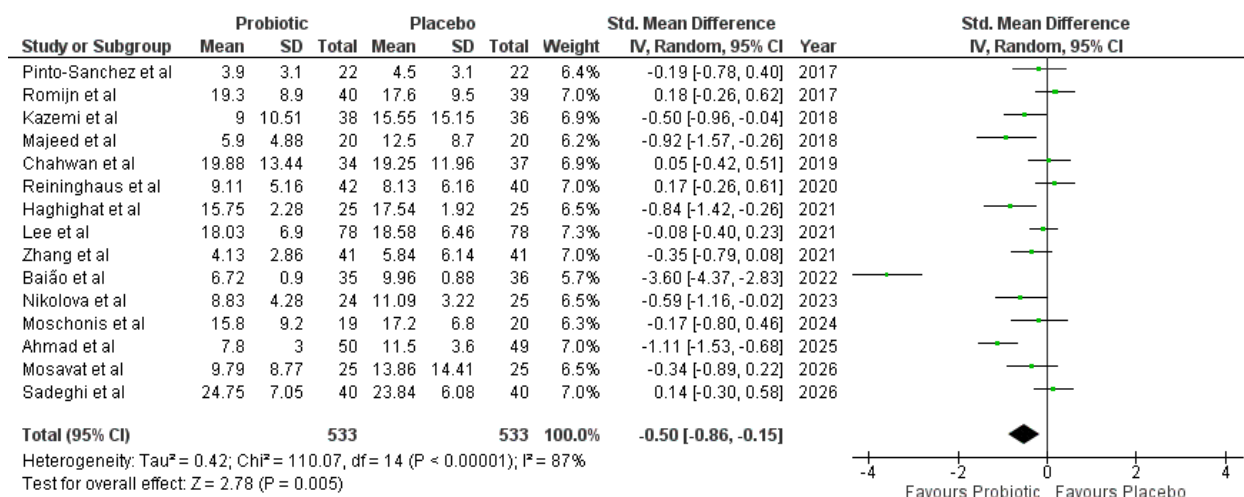


Figure 2. Forest plot of the effect of probiotics versus placebo on depressive symptoms (random-effects model)

In all the 15 included randomized controlled trials, depressive symptom outcomes were reported using validated scales which included Beck Depression Inventory-II (BDI-II), Hamilton Depression Rating Scale (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), Hospital Anxiety and Depression Scale-Depression subscale (HADS-D), and Patient Health Questionnaire-9 (PHQ-9).

Meta-analysis was done using end of treatment scores which demonstrated that probiotic interventions were associated with a reduction in depressive symptoms compared with placebo which was statistically significant. The pooled standardized mean difference (Hedges' g) was -0.50 (95% CI: -0.86 to -0.15), which

indicated a moderate effect size in favor of probiotics. Also, substantial statistical heterogeneity was found to be present across studies ($I^2 = 87\%$, $p < 0.00001$), suggesting variability in effect sizes, which could be attributed to differences in study populations, probiotic strains and intervention protocols.

The overall effect was found to be statistically significant ($Z = 2.78$, $p = 0.005$), which indicated towards the efficacy of probiotics in reducing depressive symptoms. The direction of effect was observed to be consistent across majority of the included studies, with most of them favoring probiotic interventions.

Subgroup Analysis

Table 3. Subgroup Classification

Study ID	Severity (Minimal to Mild vs Moderate to Severe)	Duration (<8 weeks vs ≥8 weeks)
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S1	Minimal to Mild	<8 weeks
S2	Moderate to Severe	≥8 weeks
S3	Moderate to Severe	≥8 weeks
S4	Moderate to Severe	≥8 weeks
S5	Moderate to Severe	≥8 weeks
S6	Moderate to Severe	<8 weeks
S7	Minimal to Mild	≥8 weeks
S8	Minimal to Mild	≥8 weeks
S9	Moderate to Severe	≥8 weeks
S10	Moderate to Severe	<8 weeks
S11	Moderate to Severe	≥8 weeks
S12	Minimal to Mild	≥8 weeks
S13	Minimal to Mild	≥8 weeks
S14	Moderate to Severe	<8 weeks
S15	Minimal to Mild	≥8 weeks

Subgroup analyses were performed based on baseline severity of depression and duration of intervention.

Severity of Depression



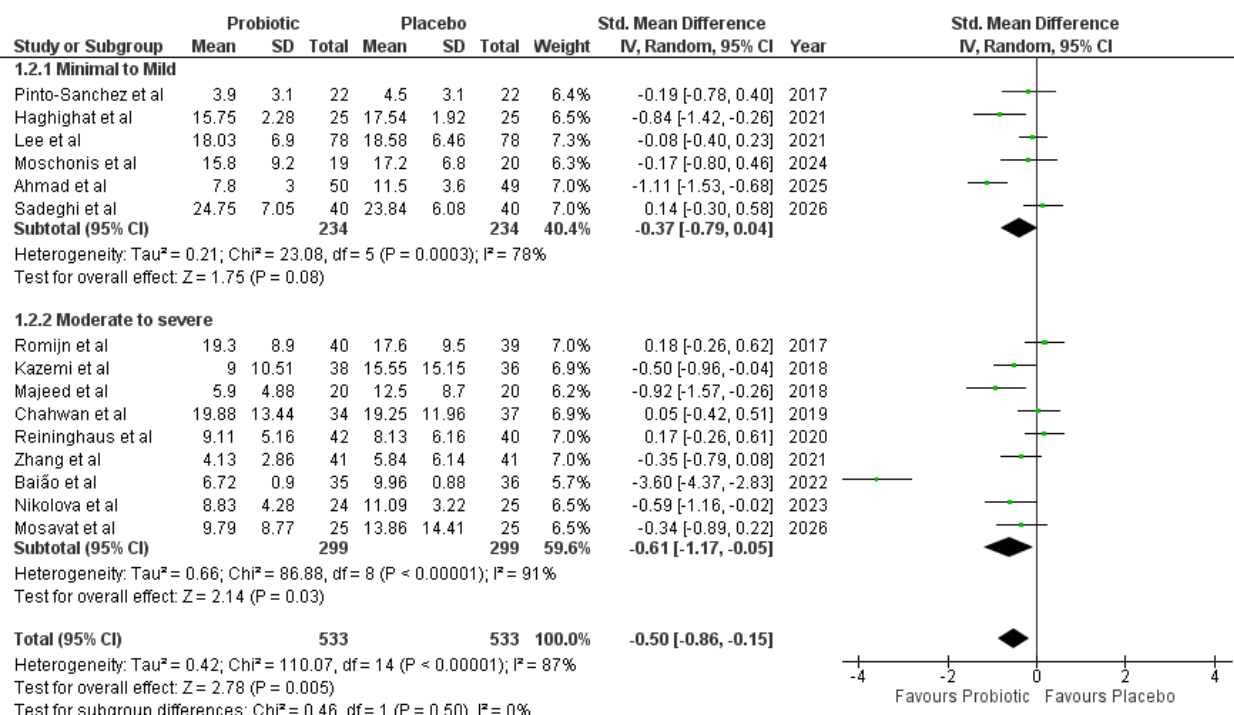


Figure 3. Subgroup analysis of the effect of probiotics on depressive symptoms based on baseline depression severity

On the basis of baseline severity of depression, subgroup analysis was conducted by categorizing the included studies into minimal to mild ($n = 6$) and moderate to severe ($n = 9$) subgroups.

In the minimal to mild subgroup, probiotic interventions were associated with a reduction in depressive symptoms (Hedges' $g = -0.37$; 95% CI: -0.79 to 0.04). However, the effect was not found to be statistically significant ($p = 0.08$). also, substantial heterogeneity was observed within this subgroup ($I^2 = 78\%$). In contrast, the moderate to severe subgroup

showed a statistically significant reduction in depressive symptoms with probiotic supplementation (Hedges' $g = -0.61$; 95% CI: -1.17 to -0.05 ; $p = 0.03$). High heterogeneity ($I^2 = 91\%$) was exhibited by this subgroup as well.

Despite the differences in statistical significance, the test for subgroup differences was not found to be statistically significant ($\chi^2 = 0.46$, $p = 0.50$), thus indicating that the effect of probiotics did not differ significantly between severity levels.

Duration of Intervention

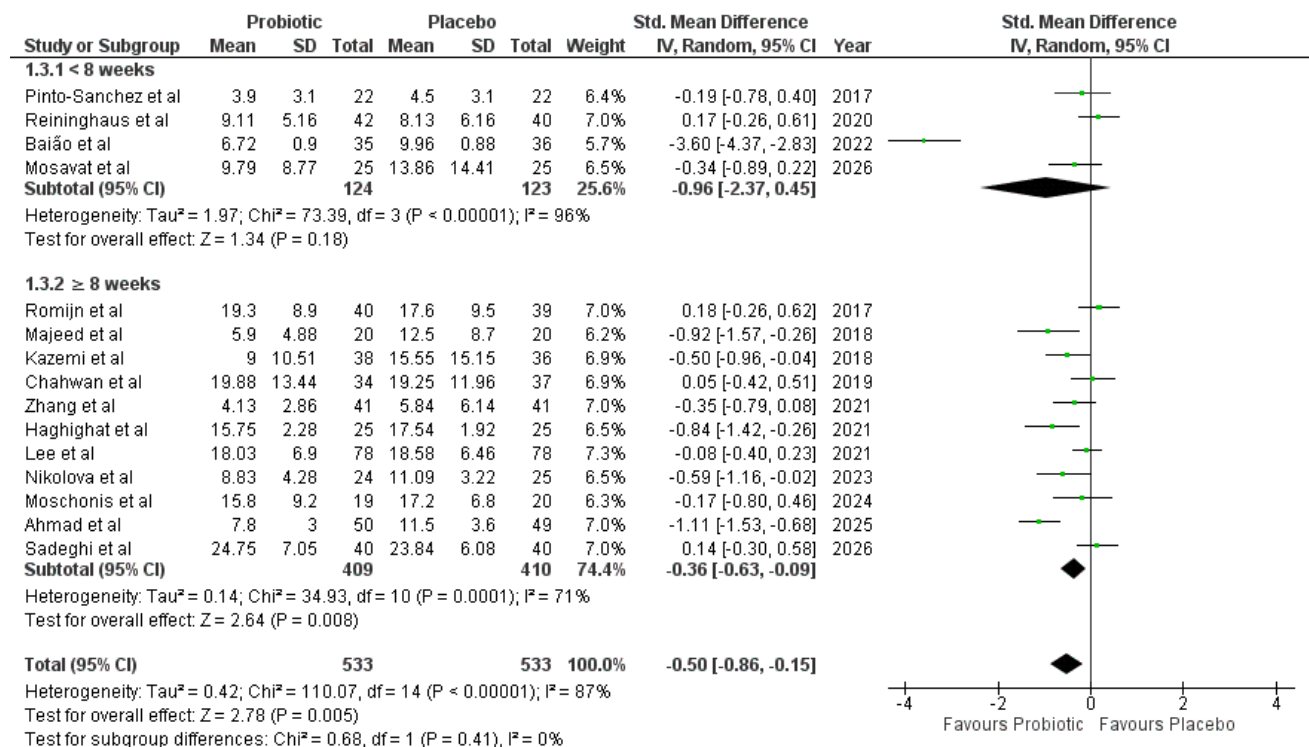


Figure 4. Subgroup analysis of the effect of probiotics on depressive symptoms based on duration of intervention

Subgroup analysis on the basis of duration of intervention was conducted by categorizing studies into short duration (<8 weeks; $n = 4$) and long duration (≥ 8 weeks; $n = 11$) interventions.

In the short duration subgroup (<8 weeks), probiotic interventions were associated with a reduction in depressive symptoms which was not found to be statistically significant (Hedges' $g = -0.96$; 95% CI: -2.37 to 0.45 ; $p = 0.18$). This subgroup demonstrated considerable heterogeneity ($I^2 = 96\%$). In contrast, the

long-duration subgroup (≥ 8 weeks) showed a statistically significant reduction in depressive symptoms with probiotic supplementation (Hedges' $g = -0.36$; 95% CI: -0.63 to -0.09 ; $p = 0.008$), with substantial heterogeneity ($I^2 = 71\%$).

However, the test for subgroup differences was not statistically significant ($\chi^2 = 0.68$, $p = 0.41$), indicating that the duration of intervention did not significantly modify the effect of probiotics.

Publication Bias



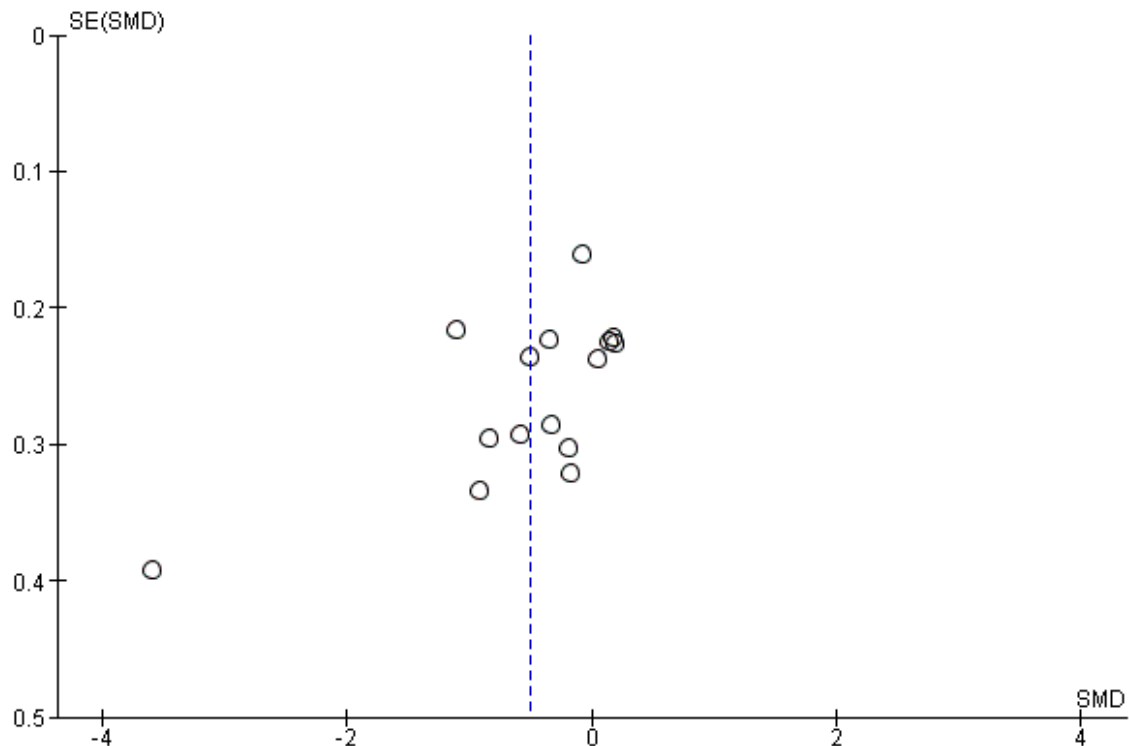


Figure 5. Funnel plot assessing publication bias for the effect of probiotics on depressive symptoms

On visual inspection of the funnel plot, the distribution of studies appeared to be moderately symmetrical around the pooled effect size. This suggests a low to moderate risk of publication bias. However, slight asymmetry was observed, with a relative paucity of studies on one side of the plot and the presence of a potential outlier with a larger effect size. This may indicate the possibility of small study effects or

selective publication of studies with more pronounced outcomes.

As the number of included studies was relatively small ($n = 15$) and substantial heterogeneity was observed across studies, a formal statistical test for funnel plot asymmetry was not performed. Overall, while no strong evidence of publication bias was detected, the possibility of its presence cannot be entirely excluded.

Risk of Bias Assessment

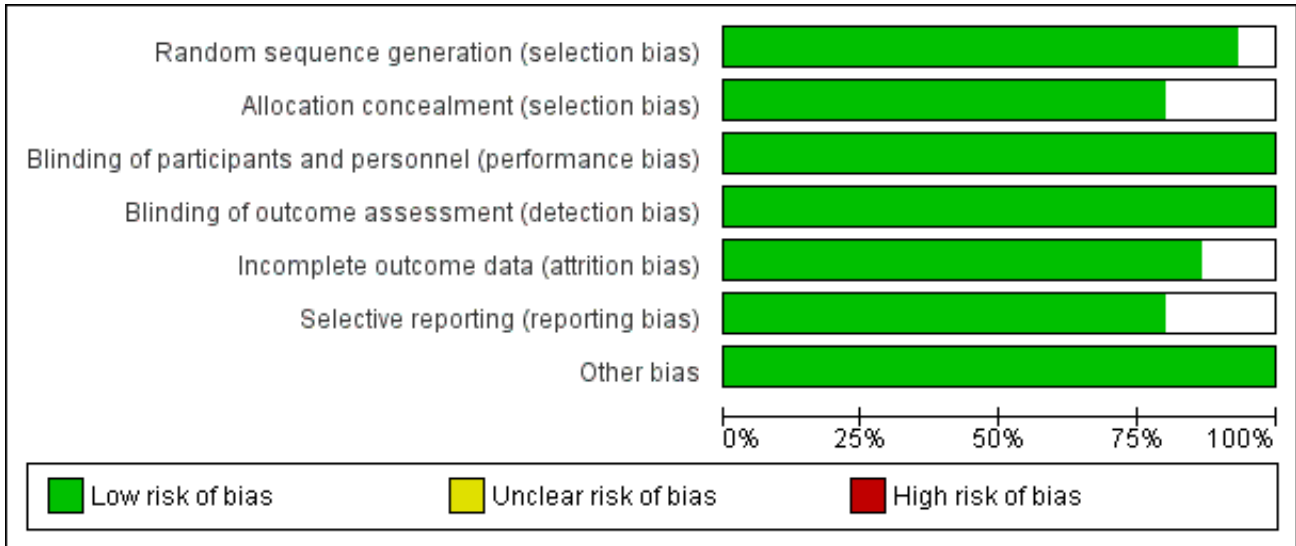


Figure 6. Risk of bias graph: authors’ judgments about each risk of bias item presented as percentages across all included studies

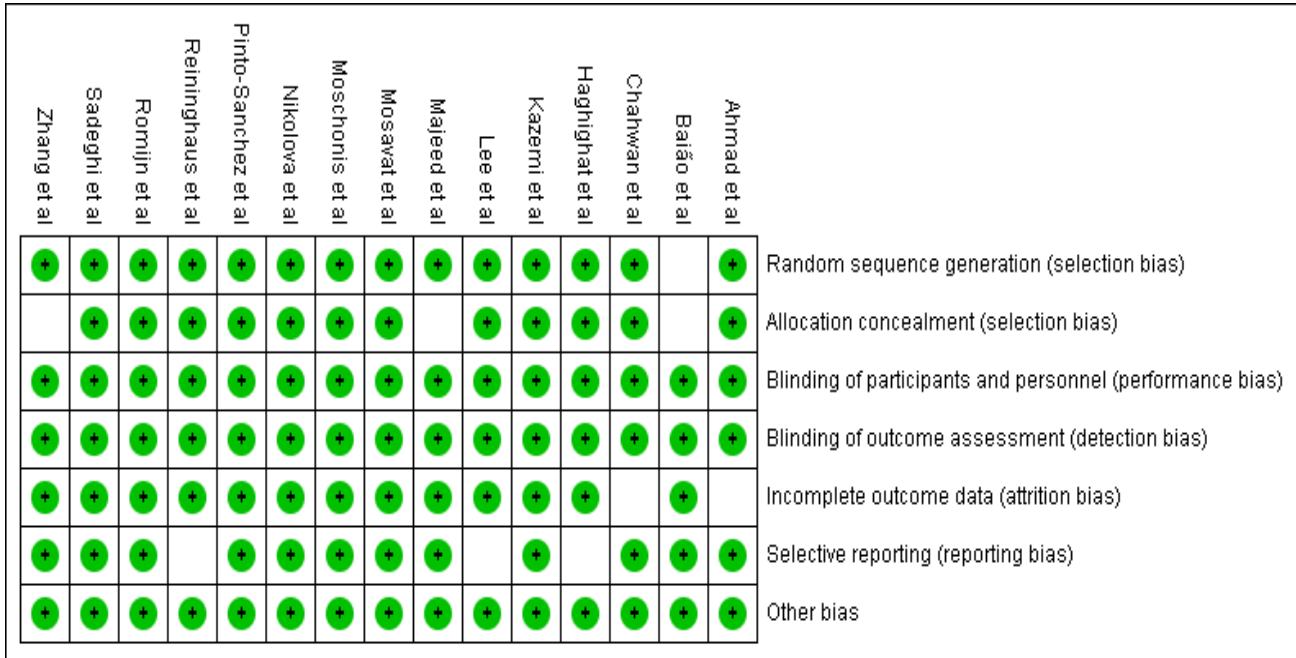


Figure 7. Risk of bias summary: authors’ judgments about each risk of bias item for each included study

The risk of bias of the included studies was assessed using the Cochrane Risk of Bias (RoB) tool. Low risk of bias was observed for the randomization process in most studies, with only a small proportion of studies showing some concerns regarding selection bias due to insufficient reporting of allocation concealment methods. All studies were observed to be at low risk of bias for blinding of participants and personnel and blinding of outcome assessment which indicated towards robust methodological design, thus minimizing the likelihood of performance and detection biases. Majority of the studies were observed to be at low risk of bias for incomplete outcome data, although a small number showed some concerns due to incomplete reporting or potential attrition related issues. Selective

reporting bias was also low in most of the studies, with a few studies demonstrating some concerns due to lack of clarity regarding pre-specified outcomes.

Overall, majority of the studies demonstrated a low risk of bias across most domains. Seven studies were classified as having low risk of bias, while eight studies were found to be having some concern in one of the domains. None of the studies were observed as having a high risk of bias. These findings suggest that the overall quality of the studies is acceptable and that the results of our meta-analysis are unlikely to be significantly affected by methodological limitations.

DISCUSSION

This systematic review and meta-analysis included 15 randomized controlled trials and demonstrated that probiotic supplementation was linked to a statistically significant reduction in depressive symptoms, with a moderate overall effect size. These findings suggest that probiotics could be a beneficial adjunctive treatment approach in the management of depression. Modulation of the gut-brain axis by probiotics may be a possible explanation for their observed antidepressant effects. Evidence from previous studies shows that gut microbiota influence brain function through multiple pathways that include neural, immune and endocrine mechanisms. It has also been found that probiotics can regulate inflammatory responses, reduce pro-inflammatory cytokines and influence neurotransmitter production, which include serotonin and gamma-aminobutyric acid (GABA) [4, 25]. Also, an imbalance of gut microbiota has been consistently found to be associated with depression, which further supports the potential of microbiome-focused treatments [26].

In our study, subgroup analyses showed that probiotics had a stronger and statistically significant effect in individuals with moderate to severe depression compared to those with minimal to mild depressive symptoms. This finding suggests that probiotics may exert a greater clinical benefit in populations who are more severely affected with depression. Similarly, it was observed that probiotics demonstrated significant effects in studies with intervention durations of ≥ 8 weeks, while studies with shorter intervention durations of < 8 weeks did not show statistical significance. This supports the idea that modulation of gut microbiota with probiotics may need longer exposure to achieve measurable clinical benefits. However, these observations should be interpreted with caution as the tests for subgroup differences were not found to be statistically significant.

Substantial heterogeneity was observed across studies, even though the overall results were encouraging. This heterogeneity could be attributed to various factors which include differences in participant characteristics, probiotic strains used, dosages, formulations, treatment durations and outcome measures. The included studies had utilized several combinations of probiotics, ranging from single-strain to complex multi-strain formulations, which may differ in their mechanisms of action and efficacy. Additionally, the inclusion of both clinical and subclinical populations, along with individuals with comorbid conditions, may have contributed to variability in the treatment response of participants.

The findings of this study align with the previous systematic reviews, which have reported modest but significant effects of probiotics on alleviating depressive symptoms [9, 27]. However, this study builds on the existing research by including more recent randomized controlled trials and conducting thorough

subgroup analyses based on the severity of depression and duration of treatment.

The risk of bias assessment indicated that the overall methodological quality of included studies was moderate to high, with most of the studies demonstrating low risk of bias across domains. This strengthens the validity of our findings. Furthermore, analysis of the funnel plot for assessment of publication bias did not suggest any strong evidence of asymmetry, although the possibility of small study effects cannot be completely ruled out.

Several limitations should be taken into account while interpreting the results of this review. First, the generalizability of the overall effect size may be limited due to a high degree of heterogeneity across the included studies. Second, differences in probiotic strains and dosages prevent us from identifying the most effective formulation in reducing depressive symptoms. Third, the long-term impact of probiotic use remains unclear as most of the studies had relatively short durations. Finally, some of the included studies had participants with subclinical depression which may have diluted the observed effect size.

From a clinical point of view, probiotics could be a safe, accessible and well-tolerated adjunctive treatment option for individuals with depressive symptoms. Future research should focus on identifying optimal probiotic strains, dosing regimens, and treatment durations, as well as investigating their mechanisms of action and long-term effects on depression.

CONCLUSION

With this systematic review and meta-analysis, we observed that probiotic supplementation is associated with a moderate and statistically significant reduction in depressive symptoms. The beneficial effects were found to be more in individuals with moderate to severe depression and in those taking the intervention for a longer duration, although subgroup differences were not found to be statistically significant. Despite substantial heterogeneity, the overall quality of evidence was acceptable. Thus, we conclude that probiotics may represent a promising adjunctive approach in the management of depression. However, further large-scale, well-designed randomized controlled trials are required to establish optimal formulations, dosing, and long-term efficacy.

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REFERENCES

1. World Health Organization. Depressive disorder (depression). 2025.



2. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, *et al.* Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163(11):1905–17.
3. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, *et al.* Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet*. 2018 Apr 7;391(10128):1357–66.
4. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nat Rev Neurosci*. 2012 Oct;13(10):701–12.
5. Dinan TG, Cryan JF. The Microbiome-Gut-Brain Axis in Health and Disease. *Gastroenterol Clin North Am*. 2017 Mar 1;46(1):77–89.
6. Kelly JR, Borre Y, O' Brien C, Patterson E, El Aidy S, Deane J, *et al.* Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat. *J Psychiatr Res*. 2016 Nov 1;82:109–18.
7. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, *et al.* Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol*. 2014;11(8):506–14.
8. Wallace CJK, Milev R. The effects of probiotics on depressive symptoms in humans: a systematic review. *Ann Gen Psychiatry*. 2017 Feb 20;16(1).
9. Ng QX, Peters C, Ho CYX, Lim DY, Yeo WS. A meta-analysis of the use of probiotics to alleviate depressive symptoms. *J Affect Disord*. 2018 Mar 1;228:13–9.
10. Pinto-Sanchez MI, Hall GB, Ghajar K, Nardelli A, Bolino C, Lau JT, *et al.* Probiotic *Bifidobacterium longum* NCC3001 Reduces Depression Scores and Alters Brain Activity: A Pilot Study in Patients With Irritable Bowel Syndrome. *Gastroenterology*. 2017 Aug 1;153(2):448–459.e8.
11. Romijn AR, Rucklidge JJ, Kuijter RG, Frampton C. A double-blind, randomized, placebo-controlled trial of *Lactobacillus helveticus* and *Bifidobacterium longum* for the symptoms of depression. *Aust N Z J Psychiatry*. 2017 Aug 1;51(8):810–21.
12. Nikolova VL, Cleare AJ, Young AH, Stone JM. Acceptability, Tolerability, and Estimates of Putative Treatment Effects of Probiotics as Adjunctive Treatment in Patients with Depression: A Randomized Clinical Trial. *JAMA Psychiatry*. 2023 Aug 2;80(8):842–7.
13. Moschonis G, Sarapis K, Resciniti S, Hall R, Yim K, Tonkovic M, *et al.* Evaluation of a probiotic blend on psychosocial health and biomarkers of inflammatory, immune and stress response in adults with subthreshold depression: A double-blind, randomised, placebo-controlled trial. *Br J Nutr*. 2024;
14. Ahmad SR, AlShahrani AM, Kumari A. Effects of Probiotic Supplementation on Depressive Symptoms, Sleep Quality, and Modulation of Gut Microbiota and Inflammatory Biomarkers: A Randomized Controlled Trial. *Brain Sci*. 2025 Jul 1;15(7).
15. Mosavat SH, Sahraian A, Kalani M, Namjoyan F, Ghasemi Y. Effect of probiotic supplement on improvement of depressive symptoms in patients with substance-induced depressive disorder: a randomized, double-blind, placebo-controlled clinical trial. *BMC Psychiatry*. 2026 Mar 13;26(1):334.
16. Sadeghi N, Shams S, Mirloshian R-S, Haerifar F, Bakhshi-Kashi M, Ghaderi A. The effect of probiotics on anxiety, depression, nicotine dependence, and metabolic biomarkers in smokers: a randomized clinical trial. *BMC Complement Med Ther*. 2025 Dec 29;
17. Kazemi A, Noorbala AA, Azam K, Eskandari MH, Djafarian K. Effect of probiotic and prebiotic vs placebo on psychological outcomes in patients with major depressive disorder: A randomized clinical trial. *Clin Nutr*. 2019 Apr 1;38(2):522–8.
18. Majeed M, Nagabhushanam K, Arumugam S, Majeed S, Ali F. *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 Nutr Res*. 2018 Jul 4;62.
19. Chahwan B, Kwan S, Isik A, van Hemert S, Burke C, Roberts L. Gut feelings: A randomised, triple-blind, placebo-controlled trial of probiotics for depressive symptoms. *J Affect Disord*. 2019 Jun 15;253:317–26.
20. Reininghaus EZ, Platzer M, Kohlhammer-Dohr A, Hamm C, Mörl S, Bengesser SA, *et al.* Provit: Supplementary probiotic treatment and vitamin b7 in depression—a randomized controlled trial. *Nutrients*. 2020 Nov 1;12(11):1–17.
21. Haghighat N, Mohammadshahi M, Shayanpour S, Haghighizadeh M, Rahmdel S, Rajaei M. The Effect of Synbiotic and Probiotic Supplementation on Mental Health Parameters in Patients Undergoing Hemodialysis: A Double-blind, Randomized, Placebo-controlled Trial. *Indian J Nephrol*. 2021;31(2):149.
22. Lee HJ, Hong JK, Kim JK, Kim DH, Jang SW, Han SW, *et al.* Effects of probiotic nvp-1704 on mental health and sleep in healthy adults: An 8-week randomized, double-blind, placebo-controlled trial. *Nutrients*. 2021 Aug 1;13(8).
23. Zhang X, Chen S, Zhang M, Ren F, Ren Y, Li Y, *et al.* Effects of fermented milk containing *Lactocaseibacillus paracasei* strain shirota on constipation in patients with depression: A



- randomized, double-blind, placebo-controlled trial. *Nutrients*. 2021 Jul 1;13(7).
24. Baião R, Capitão LP, Higgins C, Browning M, Harmer CJ, Burnet PWJ. Multispecies probiotic administration reduces emotional salience and improves mood in subjects with moderate depression: A randomised, double-blind, placebo-controlled study. *Psychol Med*. 2023 Jun 7;53(8):3437–47.
25. Foster JA, McVey Neufeld KA. Gut–brain axis: how the microbiome influences anxiety and depression. *Trends Neurosci*. 2013 May 1;36(5):305–12.
26. Jiang H, Ling Z, Zhang Y, Mao H, Ma Z, Yin Y, *et al*. Altered fecal microbiota composition in patients with major depressive disorder. *Brain Behav Immun*. 2015 Aug 1;48:186–94.
27. Huang R, Wang K, Hu J. Effect of Probiotics on Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Nutrients*. 2016 Aug 6;8(8):483.