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Probiotics in Depression Management: Efficacy, Mechanisms and Future Directions

Learn-Han Lee[1]*

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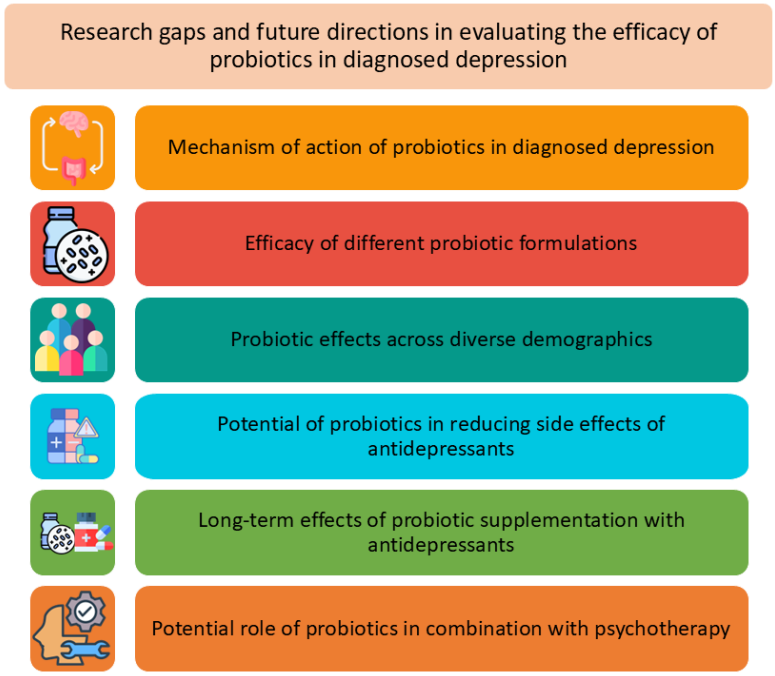
[1]Microbiome Research Group, Research Centre for Life Science and Healthcare, Nottingham Ningbo China Beacons of Excellence Research and Innovation Institute (CBI), University of Nottingham Ningbo China, Ningbo 315000

*Corresponding author: Learn-Han Lee; Microbiome Research Group, Research Centre for Life Science and Healthcare, Nottingham Ningbo China Beacons of Excellence Research and Innovation Institute (CBI), University of Nottingham Ningbo China, Ningbo 315000, China; learn-han.lee@nottingham.edu.cn

Abstract: Depression affects approximately 280 million people worldwide, representing a significant public health burden. It is characterized by persistent sadness, anhedonia, fatigue, sleep disturbances, cognitive dysfunction, and in severe cases, suicidal ideation. The pathophysiology is often attributed to neurotransmitter imbalances, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, and inflammation. Recently, the gut-brain axis has garnered attention for its role in mood regulation, suggesting that probiotic supplementation may influence depressive symptoms through gut microbiome modulation. Therefore, this review examines recent findings and research gaps regarding the efficacy of probiotics in managing clinically diagnosed depression. Emerging research demonstrates that daily probiotic supplementation from 3×10^9 CFU to 9×10^{11} CFU for four to eight weeks in combination with antidepressants is effective in improving depressive symptoms. Effective formulations commonly included *Bifidobacteria*, *Lactobacilli*, *Lactococcus lactis*, and *Streptococcus thermophilus*. Nevertheless, significant gaps remain, particularly concerning the mechanistic pathways, comparative effectiveness, and impact across different demographics of the probiotics. Furthermore, the long-term effects of probiotic use with antidepressants, their role in reducing antidepressant side effects, and combined effects with psychotherapy are largely understudied. Addressing these gaps through standardized methodologies will enhance evaluations of probiotic strains to optimize microbiome-based treatment regimens, and ultimately improve mental health outcomes in depression management.



Graphical abstract. Summary of research gaps and future directions to determine the efficacy of probiotics in diagnosed depression.

Keywords: probiotics, major depressive disorder, depression, gut-brain axis; SDG 3 Good health and well-being

1. Introduction

Depression, otherwise known as depressive disorder encompasses a wide range of conditions such as major depressive disorder (MDD), postnatal depression, premenstrual dysphoric disorder, and seasonal affective disorder [1]. This debilitating psychiatric condition can be attributed to neurotransmitter dysregulation, genetic predisposition, and environmental factors such as chronic stress or traumatic life experiences [2, 3]. These can lead to the development of various emotional, cognitive, and physical symptoms such as persistent feelings of sadness, anhedonia, sleep disturbances, decrease in energy levels, and fluctuations in appetite or body weight [4, 5]. Moreover, this mental health disorder can be further divided into primary and secondary depression. Primary depression occurs independently, without precedence by any other psychiatric or physical disorders whereas these underlying disorders take precedence in secondary depression [1, 6]. For instance, research has shown that depression is significantly associated with chronic diseases such as diabetes, arthritis, and cardiovascular diseases [7, 8]. The physical and emotional burden of managing these health conditions can create a vicious cycle of stress which contributes to the onset or exacerbation of depression. Prolonged episodes of depression can severely impact the ability of an individual to function in daily life, often disrupting social interactions, performance in studies or work, and a decline in overall personal well-being. In more severe cases, the cumulative

impacts of the depressive symptoms can drive the emergence of suicidal ideation, increasing the risk of suicide in affected individuals [9, 10]. On a global scale, it is estimated that approximately 280 million people suffer from depression [11]. In 2021, depression accounted for 713.8 disability-adjusted life years (DALYs) per 100,000 people worldwide, underscoring its burden on public health [12].

There is no single, definitive mechanism that explains the onset of depression. Instead, multiple hypotheses have been proposed to elucidate the development of depression. These include the hypothalamic-pituitary-adrenal (HPA) axis dysfunction hypothesis, monoamine hypothesis, and inflammatory hypothesis. All three theories suggest that dysregulation in biological systems such as feedback regulation during stress response, neurotransmitter balance, and immune function contribute to the onset and progression of depression [13, 14]. Genetic factors, structural and functional brain remodeling, and environmental stress factors are also key contributors theorized in the pathophysiology of depressive disorders [15, 16]. As a result, the complexity of depression driven by the interplay of various causative factors and the heterogeneity of depression among individuals poses significant challenges for diagnosis and treatment [17]. Current pharmacological treatments target specific mechanisms of depression but often fail to cover the broad spectrum of the disease pathophysiology. For example, the use of selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) aim to target and inhibit the reuptake of serotonin and norepinephrine in the synaptic cleft to elicit antidepressive effects [15, 18]. However, the specificity of these antidepressants on neurotransmitter imbalance may not account for the dysregulations that occur in the HPA-axis or the immune system in depression. Furthermore, there are varying side effects that can occur depending on the choice of antidepressant prescribed for treatment. The common side effects are nausea, sleep disturbances, sexual dysfunction, weight gain, emotional blunting, and increased anxiety or agitation in the early stages of treatment [19, 20]. These side effects negatively impact the quality of life and medication adherence in patients with depression, and may ultimately result in treatment discontinuation [21, 22].

The limitations of traditional antidepressant therapies in addressing the full complexity of depression accompanied by their side effects have led to emerging research that explores innovative adjuncts to contemporary treatment, including the use of probiotics [23-27]. The disruption of the gut microbiome has been linked to various disease states in humans [28-30], including mental health conditions such as depression. Moreover, the gut-brain axis has been increasingly implicated in depression, as there is growing evidence which suggests that gut dysbiosis may influence mood regulation, thus playing a role in the onset of depression [31-33]. Multiple studies have postulated that changes in microbiome composition including diversity and abundance of certain bacteria in the gut are associated with depression [34, 35]. As probiotics have shown promise in treating various health conditions through gut microbiota modulation [36-38], researchers have been investigating the potential of various probiotic strains that can improve depression symptoms by targeting the gut microbiome. These probiotics, often referred to as psychobiotics, are live bacteria that confer

beneficial effects on neuronal functions by colonizing into the intestinal flora, thereby influencing the gut-brain axis to regulate mood and stress responses [39]. For example, Walden *et al.* found the use of probiotics in healthy adults resulted in improvements in mood-related questionnaires which evaluated mood, anxiety, and depression. The improvements were proposed to be associated with the alterations in the intestinal microbiota, affecting the production of neurotransmitter precursors, short-chain fatty acids (SCFAs), or other secondary metabolites. These changes could have subsequently impacted the regulation or formation of various substances involved in brain function and mood modulation [40]. However, many studies have been conducted in healthy subjects, making it difficult to extrapolate the findings to patients with diagnosed depression [41-43]. Despite this, the observed improvement in depressive symptoms with probiotic use in healthy subjects offers a promising outlook for its potential in symptom relief in clinically depressed patients.

Therefore, this review aims to explore the recent advancements in the use of probiotics for managing diagnosed depression, with a focus on their efficacy in improving depressive symptoms. Given the complexity of depression and its frequent overlap with other medical conditions, these findings provide valuable insights into how probiotics could complement existing treatments to alleviate depressive symptoms. By shedding light on the currently known effects of probiotics in managing depression, this review provides a foundation for future research into broader therapeutic roles of probiotics in treating depression.

2. Methods

The search for this review was conducted with a systematic approach whereby articles from 2019 to 2024 were retrieved from Embase, Ovid MEDLINE, PubMed, and Scopus using the key words “probiotics”, “depression”, and “randomized controlled trial”. Additional search was performed to cover the commonly used probiotics in commercial products by using the terms “*Lactobacillus*”, “*Streptococcus*”, “*Bifidobacterium*”, “*Enterococcus*”, “*Escherichia*”, and “*Bacillus*”. English articles reporting on the effects of probiotic use in diagnosed depression were considered.

3. Efficacy of probiotics in clinically diagnosed depression

Recent advancements in probiotics have revealed a compelling link between probiotics and the management of depression, driven by various mechanisms in which they modulate the gut-brain axis [39, 44]. Preliminary studies in animal models have produced promising results which demonstrate the capabilities of probiotics in relieving depression [45-48]. These findings laid the groundwork for subsequent human trials involving individuals with diagnosed depression. While existing literature in this area remains limited, current studies on probiotic effects on depression have demonstrated promising outcomes, offering a positive perspective on their potential therapeutic benefits (Table 1).

Table 1. Recent advancements in the efficacy of probiotics in clinically diagnosed depression.

Probiotic	Dosage	Depression score/severity	Probiotic effects	References
Bifidobacterium breve CCFM1025	10^{10} CFU daily for 4 weeks	HDRS-24 ≥ 14	• Significantly decreased HDRS-24, MADRS, BPRS, and GSRS scores • Significantly reduced serum serotonin turnover • Upregulation of tryptophan, 5-hydroxytryptophan, 5-HT, 5-HIAA, indole-3-acetamide, indole-3-lactic acid, and indole-3-propionic acid	[49]
Lactobacillus plantarum 299v	10×10^{9} CFU twice daily for 8 weeks	HAMD-17: 21.53±6.03	• No significant effects on depression scores • Improved cognitive functions • Decreased kynurenine concentration	[25]
Lacticaseibacillus paracasei strain Shirota	1×10^{10} CFU daily for 9 weeks	HAMD: 16.4±4.8	• No significant effects on depression scores	[50]
Lactobacillus plantarum PS128	3×10^{10} CFU twice daily for 8 weeks	HAMD-17: 20.38±5.63	• No significant effects on depression scores	[51]
Lactobacillus helveticus R0052, *Bifodobacterium longum* R0175	10×10^{9} CFU daily for 8 weeks	BDI: 14.15-21.62	• Significant decrease in BDI scores • Increased serum brain-derived neurotrophic factor levels	[52, 53]
Lactobacillus helveticus R0052, *Bifidobacterium longum* R0175	3×10^{9} CFU daily for 8 weeks	MADRS ≥ 20	• Significant decrease in MADRS, QIDS-SR16, and SHAPS scores • Greater scores reductions from baseline to week 4 compared to week 4 to 8	[54]
Streptococcus thermophilus NCIMB 30438, *Bifidobacterium breve* NCIMB 30441, *Bifidobacterium longum* NCIMB 30435, *Bifidobacterium infantis* NCIMB 30436, *Lactobacillus acidophilus* NCIMB 30442, *Lactobacillus plantarum* NCIMB 30437, *Lactobacillus paracasei* NCIMB 30439, *Lactobacillus delbrueckii subsp. bulgaricus* NCIMB 30440	9×10^{11} CFU daily for 4 weeks	HAMD: 18.93±4.78 BDI: 22.38±7.54	• Significant decrease in HAMD and BDI scores • Increased abundance of *Lactobacillus* in gut	[55]
Bifidobacterium bifidum W23, *Bifidobacterium lactis W51*, *Bifidobacterium lactis W52*, *Lactobacillus acidophilus W22*,	7.5×10^{9} CFU daily for 4 weeks	BDI-II: 30.25±8.38 HAMD: 14.75±5.56	• No significant changes in depression scores • Upregulation of *CLOCK* gene expression • Decrease in interleukin-6 proinflammatory cytokine levels	[56]

Probiotic	Dosage	Depression score/severity	Probiotic effects	References
Lactobacillus casei W56, *Lactobacillus paracasei W20*, *Lactobacillus plantarum W62*, *Lactobacillus salivarius W24*, *Lactobacillus lactis W19* *Bacillus subtilis PXN® 21*, *Bifidobacterium bifidum PXN® 23*, *Bifidobacterium breve PXN® 25*, *Bifidobacterium infantis PXN® 27*, *Bifidobacterium 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*	8×10^9 CFU daily for 4 weeks	PHQ-9: 5-19	• Reduced PHQ-9 and STAI scores	[26]
Bifodobacterium breve CCFM1025, *Bifidobacteirum longum* CCFM687, *Pediococcus acidilactici* CCFM6432	10^{10} CFU daily for 4 weeks	Mild to moderate	• Greater reduction of HAMD, MADRS, BPRS, and GSRS scores than placebo	[57]
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*,	8×10^9 CFU daily for 8 weeks	HAMD-17 ≥ 13	• Greater reductions in depressive symptoms from week 4 • Significant reductions in HAMD-17, IDS, and HAMA scores	[58]

Probiotic	Dosage	Depression score/severity	Probiotic effects	References
Lactococcus lactis, *Streptococcus thermophilus* *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Streptococcus thermophilus*	4×10^{10} CFU twice daily for 8 weeks	BDI-II: 30.78±9.55	• Significant decrease in depression scores at week 4, but not at week 8 and at follow-up at week 16	[59]
Lactobacillus acidophilus, *Bifidobacterium bifidus*, *Lactobacillus rutri*, *Lactobacillus fermentum*	4×10^{9} CFU daily for 8 weeks	HDRS ≥ 20	• Significant decrease in HDRS scores • Significant improvements in sexual function	[60]
Bifidobacterium bifidum W23, *Bifidobacterium lactis* W51, *Bifidobacterium lactis* W52, *L. acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19, *Lactococcus lactis* W58	1×10^{10} CFU daily for 8 weeks	BDI ≥ 12	• No significant effects on depression scores • Significant reduction in cognitive reactivity towards sad mood	[61]
Lactobacillus helveticus Rosell®-52, *Bifidobacterium longum* Rosell®-175	3×10^{9} CFU daily for 60 days	MADRS ≥ 13	• No significant effects on depression scores	[62]

Abbreviations: HAMD/HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; BPRS, Brief Psychiatric Rating Scale; GSRS, Gastrointestinal Symptom Rating Scale; BDI, Beck Depression Inventory; QIDS-SR16, Quick Inventory of Depressive Symptomatology; SHAPS, Snaith-Hamilton Pleasure Scale; PHQ-9, Patient Health Questionnaire-9; STAI, Spielberger State-Trait Anxiety Inventory; IDS, Inventory of Depressive Symptomatology; HAMA, Hamilton Anxiety Rating Scale.

3.1. Use of probiotics alone in the management of depression

There is increasing interest in the utilization of probiotics as a standalone therapeutic approach to manage depression due to their potential to provide symptom relief without the side effects that are often associated with antidepressants. In addition, the use of probiotics in patient populations where the use of antidepressants is not recommended, such as pregnant or breastfeeding women, individuals under 18 years old, and those with comorbidities that increase the risk of adverse drug interactions could be beneficial. Probiotics may be an alternative to address the depressive symptoms while minimizing the risk of side effects or complications. Wallace *et al.* tested the efficacy of a combination probiotic supplement containing *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 marketed as CEREBIOME® in ten treatment-naïve moderate MDD patients. The supplement was given as one sachet of 3×10^9 colony forming units (CFU) in lyophilized powder once daily for 8 weeks. Upon comparing depressive symptomology from baseline using the Montogmery-Åsberg Depression Rating Scale (MADRS) and the Quick Inventory of Depressive Symptomatology (QIDS-16), the depression symptoms significantly improved from baseline to week 4, but did not improve significantly from week 4 to week 8. Moreover, similar results were reported when measuring anhedonia and anxiety, whereby significant improvements were observed in the first four weeks of intervention, followed by non-significant improvements in the subsequent weeks. Interestingly, significant improvements in sleep quality emerged only after the fourth week until the eighth week of intervention [54]. This suggests that probiotics may exert more immediate effects on mood, anxiety, and anhedonia while longer-term use might be required to observe significant improvements in sleep quality. Additionally, enhancement in sleep quality could be secondary to the improvements in depressive symptoms, rather than a direct effect of the probiotics on sleep disturbances.

In a separate study by Strodl *et al.*, although the outcome measures were measured with different scales, the overall results show similarity to that of Wallace *et al.* whereby depressive symptoms were improved. Strodl *et al.* utilized a combination probiotic consisting 2 ×1010 CFU/capsule of *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, and *Streptococcus thermophilus*, 1600mg of magnesium orotate, and 1500mg of coenzyme Q10 which was associated significant reduction in MDD diagnosis and depressive symptoms in the test subjects. The study was conducted across an 8-week intervention period with a follow-up period until week 16. The intervention group (n=58) saw significant reductions in depression diagnosis at 8 weeks but the results were not maintained at week 16. In addition, significant improvements in depressive symptoms measured by BDI-II were recorded at week 4 in the probiotic group compared to placebo (n=62) but were insignificant in weeks 8 and 16 [52]. This shows that the probiotic exhibited its strongest effect at week 4, and prolonged treatment of longer than 8 weeks may be required to sustain the beneficial effects. The anti-depressive effects of the probiotic could have been amplified with the co-supplementation of magnesium orotate and coenzyme Q10.

In contrast, Chahwan *et al.* found no significant differences between treatment with probiotics and placebo in subjects that were divided into two groups; mild or moderate depression, and severe depression. Their study involved 71 participants who were not taking any other medication and were instructed to consume the combination probiotic, Ecologic® Barrier. The total cell counts in the probiotic amounted to 1×10^{10} CFU/day of *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W51, *B. lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19, and *L. lactis* W58. At the end of the 8-week trial, there were improvements in Beck Depression Index – Second Edition (BDI-II), Depression Anxiety Stress Scale – 21 Items (DASS-21), and Beck Anxiety Inventory (BAI) in the probiotic group, but the results were not significant [61]. Microbiota data analyses performed using stool samples from 22 participants from the probiotic and 21 from placebo also showed no significant differences for alpha or beta diversity and relative abundance of bacterial taxa [61]. However, in the group with mild or moderate depression, there was a significant reduction in cognitive reactivity towards sad mood after receiving the intervention. These effects were not observed in the group with severe depression, suggesting the use of the probiotic in mild to moderate depression to improve cognitive reactivity. In addition, in the one-month follow-up analyses, the probiotic group was more likely to present with subclinical or no depression diagnosis, indicating the prolonged effects of the intervention even after the intervention period [61]. Nevertheless, the lack of significant reduction of symptoms in the probiotic group suggests that the use of probiotics alone is insufficient to elicit an effect in depressed patients.

3.2. Probiotics as an adjunct to antidepressants in depression

As data from clinical trials with probiotics alone in the treatment of depression remain inconclusive, researchers have shifted their focus toward investigating the potential of probiotics as an adjunct to antidepressant therapy [49, 55, 57]. This pivot aims to investigate whether the impact of probiotics on the gut microbiota and gut-brain axis can translate into improved therapeutic efficacy of antidepressants, thereby enhancing treatment outcomes. From the search conducted, literature on the effects of probiotics as adjuncts to antidepressants in diagnosed depression remains limited, and existing studies have produced mixed results, thus indicating the need for further investigation.

For instance, Schaub *et al.* investigated the efficacy of the high-dose probiotic, Vivomixx® as an adjunct to antidepressants. The supplement contains eight different bacteria strains namely *Streptococcus thermophilus* NCIMB 30438, *Bifidobacterium breve* NCIMB 30441, *Bifidobacterium longum* NCIMB 30435 (reclassified as *Bifidobacterium lactis*), *Bifidobacterium infantis* NCIMB 30436 (reclassified as *B. lactis*), *L. acidophilus* NCIMB 30442, *Lactobacillus plantarum* NCIMB 30437, *Lactobacillus paracasei* NCIMB 30439, *Lactobacillus delbrueckii subsp. bulgaricus* NCIMB 30440 (reclassified as *L. helveticus*). The probiotic was given to the patients at a high dose of 9×10^{11} CFU/day for 31 days in addition to their usual treatment for depression. When depressive symptoms were assessed using the Hamilton Depression Rating Scale (HAMD), the probiotics group showed a

stronger decrease in HAMD scores. The study also identified significant associations between adherence during probiotic supplementation and remission rates i.e. patients who were adherent to the intervention protocol were more likely to stay in remission [55].

Building on these findings, another study by Tian *et al.* demonstrated that the multi-probiotic containing *B. breve* CCFM1025, *B.longum* CCFM687, and *Pediococcus acidilactici* CCFM6432 was effective in reducing depression scores after a four-week intervention of lyophilized bacteria powder (10^{10} CFU/day). In comparison to the placebo, supplementation with this probiotic resulted in significant decreases in the HAMD, MADRS, and Brief Psychiatric Rating Scale (BPRS) scores in mild to moderately depressed patients without restriction on antidepressants. In addition, when gastrointestinal (GI) symptoms of the patients were evaluated by the Gastrointestinal Symptom Rating Scale (GSRS), probiotic supplementation exhibited significant improvements than in the placebo group. These findings underscore the ameliorative effects of the multispecies probiotic in mild to moderate depression while simultaneously maintaining GI health [57].

Furthermore, one study involving Iranian women with depression found that by supplementing Lactofem, a probiotic containing *L. acidophilus*, *Bifidobacterium bifidus*, *Lactobacillus rutri*, and *Lactobacillus fermentum*, each at 2×10^9 CFU/g in a 500mg biocapsule was effective in reducing depressive symptoms. The study was conducted over two months whereby the participants were divided into two groups: the intervention group which received Lactofem in addition to SSRIs, and the control group which only received SSRIs [60]. At the end of the intervention, the group receiving Lactofem showed significant improvements in depressive symptoms, evident by the reduction in HAMD scores. Moreover, the study investigated the changes in sexual function in the participants as sexual dysfunction is a known symptom of depression and can occur following antidepressant treatment [63, 64]. They found that participants receiving Lactofem experienced improvements in sexual function and satisfaction and these results were statistically significant when compared to the control group [60]. These findings also demonstrate that probiotics may help to alleviate the bidirectional relationship between sexual dysfunction and depression, where the presence of one condition exacerbates the other [65].

Apart from multispecies probiotics, some studies explore the effects of single-strain probiotics in conjunction with antidepressants in depression management. In China, Tian *et al.* recruited 51 eligible participants with MDD to determine the efficacy of consuming 10^{10} CFU *of B. breve* CCFM1025 for four weeks on depressive and GI symptoms [49]. Similarly to previous studies, probiotic supplementation resulted in improvements to a greater extent in HAMD, MADRS, BPRS, and GSRS scores when compared to the placebo group. This indicates that single-strain probiotics may have the potential to reduce depressive symptoms and mitigate SSRI-associated GI side effects in depression treatment, similar to the benefits observed with the aforementioned studies deploying multispecies probiotics.

However, when *L. plantarum* PS128 was administered as a single-strain probiotic (two capsules of 3×10^{10} CFU daily) in MDD patients over two months, the results showed

no significant differences between the probiotic and placebo groups in terms of improvements in depression symptoms, inflammation markers, gut permeability, or gut microbiota composition [51]. Interestingly, these findings are in contrast with the open trial conducted before this study, where significant improvements in depression symptoms were detected when the patients were supplemented with *L. plantarum* PS128 [66]. The improvements in depression of the open trial were observed over time, thus the authors suggested that the effects could have been attributed to the concurrent use of antidepressants in the participants, which can take time to elicit their therapeutic effects instead of probiotic use. In a separate study, Rudzki *et al.* determined that *L. plantarum* 299v supplementation in patients with major depression showed no significant changes in depressive and anxiety symptoms [25]. The probiotic was given in two capsules of 10×10^9 CFU daily over an 8-week trial period. Despite the lack of improvement in the primary outcomes, the study observed reduced kynurenine concentrations and improved cognitive functions in the patients. Although lowered kynurenine levels are associated with antidepressant effects and enhanced cognitive performance, improvements in mood were not noted in this study [25, 67]. While the probiotic did not affect mood, its role in reducing kynurenine levels can potentially contribute to cognitive benefits.

Besides, multi-strain probiotics have also shown to have no advantage over placebo in decreasing depression scores [62]. Gawlik-Kotelnicka *et al.* reported that supplementation of 3×10^9 CFU/day of *Lactobacillus helveticus* Rosell®-52 and *Bifidobacterium longum* Rosell®-175 over 60 days did not elicit a significant response in depression symptom improvement and remission rates when compared to the placebo group. This prompted the researchers to explore the pre-treatment determinants of probiotic efficacy within the study. In essence, the study found that the more advanced the metabolic abnormalities—such as being overweight, having excessive central fat, and liver steatosis—showed less evident improvements in psychometric parameters [62]. This high-lights the role of comorbidities in influencing the efficacy of probiotics as the presence of these abnormalities may limit the effectiveness of probiotics in improving mental health outcomes.

3.3. Role of probiotic formulations in depression treatment

The effectiveness of probiotic supplementation is influenced by its formulation, encompassing factors such as the number of strains used, bacteria species included, and dosage of the supplement. The interplay of these elements determines how well the probiotic can colonize the gut, which allows the probiotic to elicit its beneficial effects, ultimately influencing physiological and psychological outcomes.

When considering probiotic formulations, an important aspect is the choice be-tween single- or multi-strain probiotics. Single-strain probiotics allow for a more targeted therapeutic approach, as specific health concerns such as depression can be directly addressed. For example, the single-strain probiotic *B. breve* CCFM1025 was found to be effective in reducing depressive symptoms in depressed patients [49]. CCFM1025 promotes the 5-hydroxytryptophan (5-HTP) and serotonin (5-HT) synthesis of the gut

enterochromaffin cells via enhancing tryptophan biosynthesis, the only precursor for 5-HTP and 5-HT [49, 68]. The probiotic enhanced serotonin production in the patients, while decreasing the 5-HT turnover in their circulation, thereby stabilizing 5-HT levels which could have contributed to the beneficial effects on symptom management in depression [49, 69]. In multi-strain probiotics, the presence of different bacterial species allows for a broader range of health benefits, such as improving mood in depression while simultaneously enhancing gut health which reduces GI symptoms [49, 57]. Moreover, in the context of managing depression, the distinct mechanisms of action of different bacterial species can amplify the therapeutic effects of probiotics. By targeting the different pathways involved in the pathophysiology of depression, multispecies probiotics offer a more comprehensive approach to treatment. For instance, Baião *et al.* reported the daily intake of a probiotic containing fourteen species of bacteria (*Bacillus subtilis* PXN® 21, *Bifidobacterium bifidum* PXN® 23, *B. breve* PXN® 25, *B. infantis* PXN® 27, *B. longum* PXN® 30, *L. acidophilus* PXN® 35, *Lactobacillus delbrueckii ssp. bulgaricus* PXN® 39, *Lactobacillus casei* PXN® 37, *L. plantarum* PXN® 47, *Lactobacillus rhamnosus* PXN® 54, *L. helveticus* PXN® 45, *Lactobacillus salivarius* PXN® 57, *Lactococcus lactis ssp. lactis* PXN® 63, *Streptococcus thermophilus* PXN® 66) for 28 days in moderate depression was effective in improving emotional processing and reducing depression scores in the Patient Health Questionnaire-9 [26]. The study suggested that the efficacy of the probiotic could be attributed to the distinct effects conferred by the diverse bacterial species, such as the modulatory effects on the central gamma-aminobutyric acid (GABA) system by *Lactobacilli* and 5-HT enhancement by *B. longum* [26]. However, it is challenging to pinpoint the exact effects attributed to each specific strain of a multispecies probiotic because each strain can influence various physiological pathways, resulting in a range of out-comes.

Furthermore, findings from the literature search indicate that specific strains used in probiotics influence their efficacy against depression, regardless of whether they are part of a single-strain or multi-strain formulation. This highlights the importance of strain selection in optimizing therapeutic outcomes for individuals with depression. For instance, a single-strain of *B. breve* CCFM1025 was effective in attenuating MDD, but a single-strain of *L. plantarum* 299v did not improve symptoms of depression [25, 49]. Similarly in multi-strain studies, the use of Lactofem conferred beneficial effects in women with depression by improving mood symptoms while the combination of *L. helveticus* Rosell®-52 and *B. longum* Rosell®-175 did not exhibit significant effects in depressed patients when compared to the placebo [60, 62]. Additionally, in a systematic review evaluating the efficacy of single-strain probiotics versus multi-strain mixtures, it was revealed that multi-strain probiotics were not more effective than single-strain probiotics when strain specificity and disease were accounted for [41]. The selection of probiotic strains and the number of strains should be guided by evidence-based practices, but the lack of literature utilizing consistent probiotic intervention and outcome measures across studies of depression complicates the efforts to compare findings effectively. The variability between studies makes it challenging to draw definitive conclusions on the efficacy of specific treatments.

Besides, the dosages of probiotics also varied among the reviewed studies as different probiotic strains may require different dosages to achieve beneficial effects [25, 26, 55, 58, 60, 62, 70]. For example, Yamanbaeva *et al.* demonstrated that a high daily dose of 9×10^{11} CFU/day for four weeks of a multi-species probiotic containing eight different bacterial species improved depressive symptoms while Tian *et al.* reported the mixture containing three probiotic strains dosed at 10^{10} CFU/day for four weeks was sufficient in ameliorating depressive symptoms [57, 71]. Notably, studies that reported significant improvements in depressive symptoms generally required four to eight weeks of intervention period was required to elicit beneficial effects [26, 55, 57-61]. This duration allows adequate time for the probiotics to exert their therapeutic benefits in the gut microbiome such as modulating neurotransmitter levels and reducing inflammation. In addition, the use of probiotics across varying doses was generally well tolerated across studies with minimal reports of adverse effects. Ultimately, a thorough understanding of these formulation nuances is crucial for optimizing probiotic therapy in depression. This facilitates a targeted approach of using an optimal probiotic dose that addresses the wide range of pathophysiological pathways associated with depression thereby maximizing beneficial effects while minimizing the risk of ineffective treatment.

4. Discussion

Recent research has delved into the role of probiotics in the management of clinically diagnosed depression as compared to earlier studies which primarily examined depressive symptoms in healthy adults or individuals experiencing stress or other depression-related symptoms without a formal diagnosis [63-69]. This review finds that current research has contributed to the growing evidence that the use of probiotics can alleviate depressive symptoms in clinically diagnosed depression. Several research gaps have been identified and are summarized in Figure 1.

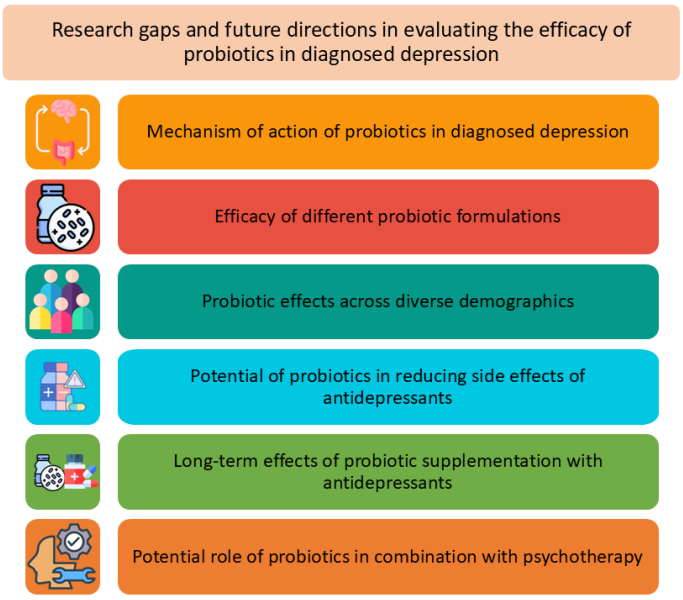


Figure 1. Summary of research gaps and future directions to determine the efficacy of probiotics in diagnosed depression.

Based on the findings, there is limited evidence to support the use of probiotics alone in the treatment of depression. However, the studies do show that the adjunct use of probiotics in antidepressant therapy can enhance the effects of symptom alleviation in depression. As the antidepressants and probiotics act on distinct pathways in depression, the treatment combination can address a broader range of physiological and psychological aspects of the mental health disorder. Current knowledge of the potential mechanisms of probiotics has been based on *in-vitro*, *in-vivo*, and animal model studies. The potential role of probiotics in depression is proposed to be multi-faceted, with various effects such as modulation of the gut-brain axis, neurotransmitter production enhancement, reduction of inflammation, stress response modulation, normalization of the HPA-axis, and restoration of gut permeability [41, 45, 69-73]. Moreover, these effects are interconnected with each other, creating a synergistic network that may enhance the therapeutic effects of probiotics in depression. For example, under conditions of stress, the HPA-axis activates cortisol secretion which can trigger the release of pro-inflammatory cytokines, alter gut permeability, and change the composition of the gut microbiota [74]. In the context of depression, these physiological changes can exacerbate symptoms when an individual is under stressful conditions. Probiotic supplementation which regulates cortisol and pro-inflammatory cytokine levels can effectively reduce stress and inflammation, leading to the alleviation of depressive symptoms [75]. Nonetheless, further research is required to elucidate the exact mechanisms of action of probiotics in diagnosed depression. It is also important to recognize that the effects may be strain-specific, thus uncovering the precise mechanisms in which each probiotic strain operates allows for optimized treatment of depressive symptoms. Future studies should incorporate outcome measures that investigate the mechanisms of probiotics, such as the measurement of alterations in neurotransmitter levels, inflammatory cytokines, cortisol levels, and gut microbiome in depression management [76-79]. By detecting changes in these markers following probiotic intervention, researchers can gain better insights into how the probiotics may influence depressive symptoms. This approach allows for the identification of symptom-specific effects associated with the probiotic strains. These properties could be harnessed to enhance treatment responses in depression.

Furthermore, evidence on whether single-strain or multi-strain probiotics offer greater benefits remains inconclusive. This is because studies have been using different strains and dosages of probiotics in diagnosed depression, making it difficult to compare the results [25, 50, 51, 55, 56, 58, 80]. Discrepancies in study design, subject demographics, and scales used to measure depression outcomes also complicate the interpretation and comparison of findings [81]. Further research could focus on comparative studies that directly evaluate the efficacy of specific strains or formulations of probiotics in treating depression. Comparing probiotics under standardized methodologies and trial protocols enables researchers to identify which strains yield the most significant therapeutic benefits. The clinical trials can then be modified to focus on specific demographics, including age, gender, depression severity, and co-morbidities to better understand how different groups may respond to probiotic interventions. The findings may also help determine whether probiotic supplementation interacts with other existing treatment regimens for other health conditions

in the participants. In addition, the effects of probiotics in reducing the side effects of antidepressants during co-administration should be explored in future studies. The potentially lowered risk of side effects associated with antidepressants due to probiotic supplementation could improve medication tolerability and adherence, thus enhancing treatment outcomes [82, 83].

Moreover, current research frequently assesses the short-term effects (4 to 8 weeks) of probiotics as an adjunct in depression management, but the duration of antidepressant treatments is typically longer to ensure stable remission [84, 85]. This highlights a crucial gap in understanding the long-term efficacy of probiotics as part of the antidepressant treatment plan. Future studies should explore the benefits of prolonged use of probiotics in depression to determine whether sustained beneficial effects can be realized to optimize treatment strategies. Besides, the integration of probiotics into psychotherapy such as cognitive behavioral therapy (CBT) or interpersonal therapy (IPT) in the management of depression could be a research area of interest. Current practices recommend both pharmacological and psychological interventions in the treatment of depressive disorders [86-88]. In mild to moderate depression, treatment usually starts with psychological interventions before initiating pharmacological treatments. Studies have shown that psychotherapy is effective not only in reducing depression symptoms but also in improving the overall quality of life in depressed patients [89-91]. Further research could explore how probiotics may complement psychotherapy and provide additional support in alleviating depression to prevent the progression of depressive disorders to greater severity.

5. Conclusions

In conclusion, recent research has highlighted the potential benefits of probiotics as an adjunct to traditional antidepressant therapies in managing clinically diagnosed depression. Daily probiotic supplementation from 3×10^9 CFU to 9×10^{11} CFU for four to eight weeks has demonstrated effectiveness with minimal adverse effects, with noticeable improvements observed as early as four weeks into treatment. The effective formulations commonly feature *L. lactis*, *S. thermophilus*, and various species of *Bifidobacteria* and *Lactobacilli*. However, significant gaps remain in our understanding of the role of probiotics in depression. Currently, the evidence base is limited regarding several areas: the mechanistic pathways underlying probiotic efficacy, comparative effectiveness of various formulations, and the impact of probiotics across diverse demographics. In addition, there is a lack in clarity on the long-term effects of probiotic supplementation in conjunction with antidepressants. The potential roles of probiotics in mitigating the side effects of antidepressants, and potential synergistic effects of probiotics when combined with psychotherapy also remain underexplored. As the focus of research continues to shift to investigating the role of probiotics in treating diagnosed depression, it is essential to address these research gaps to fully realize the true therapeutic potential of probiotics. Employing standardized methodologies will ensure accurate evaluation of the efficacy of different probiotic strains, optimize strain selection, and facilitate the development of effective treatment regimens. This approach will maximize the potential beneficial effects of probiotics in alleviating depressive

symptoms and improving overall mental health outcomes. Nonetheless, further investigation is crucial to establish a larger evidence base that supports the integration of probiotics into comprehensive depression treatment strategies.

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References

1. Gilbert P. *Depression: The evolution of powerlessness*. 2016: Routledge.

2. Pasquini M, Berardelli I, and Biondi M. Ethiopathogenesis of depressive disorders. Clin Pract Epidemiol Ment Health 2014; 10: 166-71.

3. Tafet GE and Nemeroff CB. The Links Between Stress and Depression: Psychoneuroendocrinological, Genetic, and Environmental Interactions. J Neuropsychiatry Clin Neurosci 2016; 28(2): 77-88.

4. Paykel ES. Basic concepts of depression. Dialogues Clin Neurosci 2008; 10(3): 279-289.

5. McCarter T. Depression overview. Am Health Drug Benefits 2008; 1(3): 44-51.

6. Weissman MM, Pottenger M, Kleber H, *et al*. Symptom Patterns in Primary and Secondary Depression: A Comparison of Primary Depressives With Depressed Opiate Addicts, Alcoholics, and Schizophrenics. Arch Gen Psychiatry 1977; 34(7): 854-862.

7. Lotfaliany M, Bowe SJ, Kowal P, *et al*. Depression and chronic diseases: Co-occurrence and communality of risk factors. J Affect Disord 2018; 241: 461-468.

8. Wang Z, Yang H, Guo Z, *et al*. Socio-demographic characteristics and co-occurrence of depressive symptoms with chronic diseases among older adults in China: the China longitudinal ageing social survey. BMC Psychiatry 2019; 19(1): 310.

9. Gijzen MWM, Rasing SPA, Creemers DHM, *et al*. Suicide ideation as a symptom of adolescent depression. a network analysis. J Affect Disord 2021; 278: 68-77.

10. Harwitz D and Ravizza L. Suicide and depression. Emerg Med Clin N Am 2000; 18(2): 263-271.

11. World Health Organization (WHO). Depressive disorder (depression). 2023 [Accessed 23 Sep 2024]; Available from: https://www.who.int/news-room/fact-sheets/detail/depression.

12. Dattani S, Rodés-Guirao L, Ritchie H, *et al*. Mental Health. 2023 [Accessed 23 Sep 2024]; Available from: https://ourworldindata.org/mental-health.

13. Tian H, Hu Z, Xu J, *et al*. The molecular pathophysiology of depression and the new therapeutics. MedComm 2022; 3(3): e156.

14. Otte C, Gold SM, Penninx BW, *et al*. Major depressive disorder. Nat Rev Dis Primers 2016; 2(1): 16065.

15. Cui L, Li S, Wang S, *et al*. Major depressive disorder: hypothesis, mechanism, prevention and treatment. Signal Transduct Target Ther 2024; 9(1): 30.

16. Jesulola E, Micalos P, and Baguley IJ. Understanding the pathophysiology of depression: From monoamines to the neurogenesis hypothesis model - are we there yet? Behav Brain Res 2018; 341: 79-90.

17. Athira KV, Bandopadhyay S, Samudrala PK, *et al*. An Overview of the Heterogeneity of Major Depressive Disorder: Current Knowledge and Future Prospective. Curr Neuropharmacol 2020; 18(3): 168-187.

18. Kupfer DJ. The pharmacological management of depression. Dialogues Clin Neurosci 2005; 7(3): 191-205.

19. Cascade E, Kalali AH, and Kennedy SH. Real-World Data on SSRI Antidepressant Side Effects. Psychiatry (Edgmont) 2009; 6(2): 16-8.

20. Wang S-M, Han C, Bahk W-M, *et al*. Addressing the Side Effects of Contemporary Antidepressant Drugs: A Comprehensive Review. CMJ 2018; 54(2): 101-112.

21. Marasine NR and Sankhi S. Factors Associated with Antidepressant Medication Non-adherence. Turk J Pharm Sci 2021; 18(2): 242-249.

22. Unni EJ, Gupta S, and Sternbach N. Reasons for non-adherence with antidepressants using the Medication Adherence Reasons Scale in five European countries and United States. J Affect Disord 2024; 344: 446-450.

23. Musazadeh V, Zarezadeh M, Faghfouri AH, *et al*. Probiotics as an effective therapeutic approach in alleviating depression symptoms: an umbrella meta-analysis. Crit Rev Food Sci Nutr 2023; 63(26): 8292-8300.

24. Jach ME, Serefko A, Szopa A, *et al*. The Role of Probiotics and Their Metabolites in the Treatment of Depression. Molecules 2023; 28(7): 3213.

25. Rudzki L, Ostrowska L, Pawlak D, *et al*. Probiotic *Lactobacillus Plantarum* 299v decreases kynurenine concentration and improves cognitive functions in patients with major depression: A double-blind, randomized, placebo controlled study. Psychoneuroendocrinology 2019; 100: 213-222.

26. Baião R, Capitão LP, Higgins C, *et al*. Multispecies probiotic administration reduces emotional salience and improves mood in subjects with moderate depression: a randomised, double-blind, placebo-controlled study. Psychol Med 2023; 53(8): 3437-3447.

27. Tang EK, Loo KY, Thye AYK, *et al*. The Impact of Antidepressants on Gut Microbiome and Depression Management. Prog Microbes Mol Biol 2024; 7(1): a0000446.

28. El Mazouri S, Aanniz T, Bouyahya A, *et al*. Gut Microbiota in Autism Spectrum Disorder: A Systematic Review. Prog Microbes Mol Biol 2024; 7(1).

29. Jazuli I, Jazeel A, Selvaratnam L, *et al*. Navigating the Role and Approach of Gut Microbiota in Addressing Alzheimer's Disease Pathogenesis. Prog Microbes Mol Biol 2024; 7(1).

30. Kandasamy S, Letchumanan V, Hong KW, *et al*. The Role of Human Gut Microbe *Ruminococcus gnavus* in Inflammatory Diseases. Prog Microbes Mol Biol 2023; 6(1).

31. Evrensel A and Ceylan ME. The Gut-Brain Axis: The Missing Link in Depression. Clin Psychopharmacol Neurosci 2015; 13(3): 239-44.

32. Nanthakumaran S, Sridharan S, Somagutta MR, *et al*. The Gut-Brain Axis and Its Role in Depression. Cureus 2020; 12(9): e10280.

33. Kong GY-E, Letchumanan V, Tan LT-H, *et al*. Gut microbiome in obsessive compulsive disorder: potential of probiotics as an adjuvant therapy. Prog Microbes Mol Biol 2022; 5(1): a0000272.

34. Radjabzadeh D, Bosch JA, Uitterlinden AG, *et al*. Gut microbiome-wide association study of depressive symptoms. Nat Commun 2022; 13(1): 7128.

35. Chen Y-h, Xue F, Yu S-f, *et al*. Gut microbiota dysbiosis in depressed women: The association of symptom severity and microbiota function. J Affect Disord 2021; 282: 391-400.

36. Sim AAXH, Cheam JY, Law JW-F, *et al*. The Ameliorative Role of Probiotics in 5-fluorouracil Induced Intestinal Mucositis. Prog Microbes Mol Biol 2023; 6(1).

37. Thye AY-K, Tan LT-H, Law JW-F, *et al*. Long COVID-19: Psychological symptoms in COVID-19 and probiotics as an adjunct therapy. Prog Microbes Mol Biol 2022; 5(1).

38. Loo K-Y, Thong JYH, Tan LT-H, *et al*. A Current Overview of Next-Generation Probiotics and Their Prospects in Health and Disease Management. Prog Microbes Mol Biol 2024; 7(1).

39. Evrensel A, Ünsalver BÖ, and Ceylan ME. *Psychobiotics*, in *Frontiers in Psychiatry: Artificial Intelligence, Precision Medicine, and Other Paradigm Shifts*, Y.-K. Kim, Editor. 2019, Springer Singapore: Singapore. p. 565-581.

40. Walden KE, Moon JM, Hagele AM, *et al*. A randomized controlled trial to examine the impact of a multi-strain probiotic on self-reported indicators of depression, anxiety, mood, and associated biomarkers. Front Nutr 2023; 10: 1219313.

41. Kim C-S, Cha J, Sim M, *et al*. 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. J Gerontol A Biol Sci Med Sci 2021; 76(1): 32-40.

42. Marotta A, Sarno E, Del Casale A, *et al*. Effects of Probiotics on Cognitive Reactivity, Mood, and Sleep Quality. Front Psychiatry 2019; 10.

43. Talbott S, Stephens B, Talbott J, *et al*. Effect of Coordinated Probiotic/Prebiotic/Phytobiotic Supplementation on Microbiome Balance and Psychological Mood State in Healthy Stressed Adults. FASEB J 2018; 32(S1): 533.85-533.85.

44. Johnson D, Thurairajasingam S, Letchumanan V, *et al*. Exploring the Role and Potential of Probiotics in the Field of Mental Health: Major Depressive Disorder. Nutrients 2021; 13(5): 1728.

45. Liu Y-W, Liu W-H, Wu C-C, *et al*. Psychotropic effects of *Lactobacillus plantarum* PS128 in early life-stressed and naïve adult mice. Brain Res 2016; 1631: 1-12.

46. Liang S, Wang T, Hu X, *et al*. Administration of *Lactobacillus helveticus* NS8 improves behavioral, cognitive, and biochemical aberrations caused by chronic restraint stress. Neuroscience 2015; 310: 561-577.

47. Abildgaard A, Elfving B, Hokland M, *et al*. Probiotic treatment reduces depressive-like behaviour in rats independently of diet. Psychoneuroendocrinology 2017; 79: 40-48.

48. Morozova M, Alekseev A, Saeidi A, *et al*. Normalization of Deviant Behavior in Muc2+/+ Mice through Dietary Incorporation of *Bacillus subtilis* Spores. Prog Microbes Mol Biol 2023; 6(1).

49. Tian P, Chen Y, Zhu H, *et al*. *Bifidobacterium breve* CCFM1025 attenuates major depression disorder via regulating gut microbiome and tryptophan metabolism: A randomized clinical trial. Brain Behav Immun 2022; 100: 233-241.

50. Zhang X, Chen S, Zhang M, *et al*. Effects of Fermented Milk Containing *Lacticaseibacillus paracasei* Strain Shirota on Constipation in Patients with Depression: A Randomized, Double-Blind, Placebo-Controlled Trial. Nutrients 2021; 13(7).

51. Lin S-KK, Kuo P-H, Hsu C-Y, *et al*. The effects of *Lactobacillus plantarum* PS128 in patients with major depressive disorder: an eight-week double-blind, placebo-controlled study. Asian J Psychiatr 2024; 101: 104210.

52. Kazemi A, Noorbala AA, Azam K, *et al*. Effect of probiotic and prebiotic vs placebo on psychological outcomes in patients with major depressive disorder: A randomized clinical trial. Clin Nutr 2019; 38(2): 522-528.

53. Heidarzadeh-Rad N, Gökmen-Özel H, Kazemi A, *et al*. Effects of a Psychobiotic Supplement on Serum Brain-derived Neurotrophic Factor Levels in Depressive Patients: A Post Hoc Analysis of a Randomized Clinical Trial. J Neurogastroenterol Motil 2020; 26(4): 486-495.

54. Wallace CJK and Milev RV. The Efficacy, Safety, and Tolerability of Probiotics on Depression: Clinical Results From an Open-Label Pilot Study. Front Psychiatry 2021; 12.

55. Schaub A-C, Schneider E, Vazquez-Castellanos JF, *et al*. Clinical, gut microbial and neural effects of a probiotic add-on therapy in depressed patients: a randomized controlled trial. Transl Psychiatry 2022; 12(1): 227.

56. Kreuzer K, Birkl-Toeglhofer AM, Haybaeck J, *et al*. PROVIT-CLOCK: A Potential Influence of Probiotics and Vitamin B7 Add-On Treatment and Metabolites on Clock Gene Expression in Major Depression. Neuropsychobiology 2024: 1-17.

57. Tian P, Zou R, Wang L, *et al*. Multi-Probiotics ameliorate Major depressive disorder and accompanying gastrointestinal syndromes via serotonergic system regulation. J Adv Res 2023; 45: 117-125.

58. Nikolova VL, Cleare AJ, Young AH, *et al*. Acceptability, Tolerability, and Estimates of Putative Treatment Effects of Probiotics as Adjunctive Treatment in Patients With Depression: A Randomized Clinical Trial. JAMA Psychiatry 2023; 80(8): 842-847.

59. Strodl E, Bambling M, Parnam S, *et al*. Probiotics and magnesium orotate for the treatment of major depressive disorder: a randomised double blind controlled trial. Sci Rep 2024; 14(1): 20841.

60. Hashemi-Mohammadabad N, Taghavi S-A, Lambert N, *et al*. Adjuvant administration of probiotic effects on sexual function in depressant women undergoing SSRIs treatment: a double-blinded randomized controlled trial. BMC Psychiatry 2024; 24(1): 44.

61. Chahwan B, Kwan S, Isik A, *et al*. Gut feelings: A randomised, triple-blind, placebo-controlled trial of probiotics for depressive symptoms. J Affect Disord 2019; 253: 317-326.

62. Gawlik-Kotelnicka O, Margulska A, Płeska K, *et al*. Metabolic Status Influences Probiotic Efficacy for Depression-PRO-DEMET Randomized Clinical Trial Results. Nutrients 2024; 16(9).

63. Chung Y-C, Jin H-M, Cui Y, *et al*. Fermented milk of *Lactobacillus helveticus* IDCC3801 improves cognitive functioning during cognitive fatigue tests in healthy older adults. J Funct Foods 2014; 10: 465-474.

64. Romijn AR, Rucklidge JJ, Kuijer RG, *et al*. A double-blind, randomized, placebo-controlled trial of *Lactobacillus helveticus* and *Bifidobacterium longum* for the symptoms of depression. Aust N Z J Psychiatry 2017; 51(8): 810-821.

65. Steenbergen L, Sellaro R, van Hemert S, *et al*. A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood. Brain Behav Immun 2015; 48: 258-264.

66. Slykerman RF, Kang J, Van Zyl N, *et al*. Effect of early probiotic supplementation on childhood cognition, behaviour and mood a randomised, placebo-controlled trial. Acta Paediatr 2018; 107(12): 2172-2178.

67. Sashihara T, Nagata M, Mori T, *et al*. Effects of *Lactobacillus gasseri* OLL2809 and α-lactalbumin on university-student athletes: a randomized, double-blind, placebo-controlled clinical trial. Appl Physiol Nutr Metab 2013; 38: 1228-35.

68. Messaoudi M, Violle N, Bisson J-F, *et al*. Beneficial psychological effects of a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in healthy human volunteers. Gut Microbes 2011; 2(4): 256-261.

69. Lee HJ, Hong JK, Kim J-K, *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; 13(8).

70. Patterson E, Griffin SM, Ibarra A, *et al*. *Lacticaseibacillus paracasei* Lpc-37® improves psychological and physiological markers of stress and anxiety in healthy adults: a randomized, double-blind, placebo-controlled and parallel clinical trial (the Sisu study). Neurobiol Stress 2020; 13: 100277.

71. Wang J, Ji H, Wang S, *et al*. Probiotic *Lactobacillus plantarum* Promotes Intestinal Barrier Function by Strengthening the Epithelium and Modulating Gut Microbiota. Front Microbiol 2018; 9.

72. Moludi J, Khedmatgozar H, Nachvak SM, *et al*. The effects of co-administration of probiotics and prebiotics on chronic inflammation, and depression symptoms in patients with coronary artery diseases: a randomized clinical trial. Nutr Neurosci 2022; 25(8): 1659-1668.

73. Lau AWY, Tan LT-H, Ab Mutalib N-S, *et al*. The chemistry of gut microbiome in health and diseases. Prog Microbes Mol Biol 2021; 4(1).

74. Cryan JF and Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci 2012; 13(10): 701-712.

75. Shi S, Zhang S, and Kong L. Effects of Treatment with Probiotics on Cognitive Function and Regulatory Role of Cortisol and IL-1β in Adolescent Patients with Major Depressive Disorder. Life 2023; 13(9): 1829.

76. Horowitz MA and Zunszain PA. Neuroimmune and neuroendocrine abnormalities in depression: two sides of the same coin. Ann N Y Acad Sci 2015; 1351(1): 68-79.

77. Haapakoski R, Mathieu J, Ebmeier KP, *et al*. Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. Brain Behav Immun 2015; 49: 206-215.

78. Ye X, Wang D, Zhu H, *et al*. Gut Microbiota Changes in Patients With Major Depressive Disorder Treated With Vortioxetine. Front Psychiatry 2021; 12.

79. Kovtun AS, Averina OV, Angelova IY, *et al*. Alterations of the Composition and Neurometabolic Profile of Human Gut Microbiota in Major Depressive Disorder. Biomedicines 2022; 10(9): 2162.

80. Schneider E, Doll JPK, Schweinfurth N, *et al*. Effect of short-term, high-dose probiotic supplementation on cognition, related brain functions and BDNF in patients with depression: a secondary analysis of a randomized controlled trial. J Psychiatry Neurosci 2023; 48(1): E23.

81. Johnson D, Letchumanan V, Thum CC, *et al*. A Microbial-Based Approach to Mental Health: The Potential of Probiotics in the Treatment of Depression. Nutrients 2023; 15(6): 1382.

82. De las Cuevas C, Peñate W, and Sanz EJ. Risk factors for non-adherence to antidepressant treatment in patients with mood disorders. Eur J Clin Pharmacol 2014; 70(1): 89-98.

83. Solmi M, Miola A, Croatto G, *et al*. How can we improve antidepressant adherence in the management of depression? A targeted review and 10 clinical recommendations. Braz J Psychiatry 2021; 43.

84. Liu X, Momen NC, Molenaar N, *et al*. Discontinuation of antidepressants: Is there a minimum time on treatment that will reduce relapse risk? J Affect Disord 2021; 290: 254-260.

85. Hu Y, Xue H, Ni X, *et al*. Association between duration of antidepressant treatment for major depressive disorder and relapse rate after discontinuation: A meta-analysis. Psychiatry Res 2024; 337: 115926.

86. Gautam S, Jain A, Gautam M, *et al*. Clinical Practice Guidelines for the management of Depression. Indian J Psychiatry 2017; 59(Suppl 1).

87. Park S-C, Oh HS, Oh D-H, *et al*. Evidence-Based, Non-Pharmacological Treatment Guideline for Depression in Korea. J Korean Med Sci 2013; 29(1): 12-22.

88. Olfson M, Blanco C, and Marcus SC. Treatment of Adult Depression in the United States. JAMA Intern Med 2016; 176(10): 1482-1491.

89. Meng Y, Li H, Wang J, *et al*. Cognitive behavioral therapy for patients with mild to moderate depression: Treatment effects and neural mechanisms. J Psychiatr Res 2021; 136: 288-295.

90. Kolovos S, Kleiboer A, and Cuijpers P. Effect of psychotherapy for depression on quality of life: meta-analysis. Br J Psychiatry 2016; 209(6): 460-468.

91. Cuijpers P, Geraedts AS, Oppen Pv, *et al*. Interpersonal Psychotherapy for Depression: A Meta-Analysis. Am J Psychiatry 2011; 168(6): 581-592.