JAMSA Journal of Asian Medical Students' Association

Probiotics as adjuvant therapy with antidepressants vs placebo to treat major depressive disorder: a systematic review and meta-analysis of randomized controlled trials

Introduction: Despite improvement in antidepressant treatment, half of the major depressive disorder (MDD) patients fail to achieve remission. Increasing evidence suggests the role of modulating the microbiome-gut-brain axis through probiotics in mental health therapy. We aimed to compare the efficacy and safety of probiotics as adjuvant therapy with antidepressants compared to placebo in patients with MDD.

Methods: A systematic literature search was performed in several databases, such as PubMed, Cochrane, EBSCOHost, CINAHL, Scopus, and Google Scholar from inception until November 18th 2022. The literature search aimed to find clinical trials that tested the effectiveness of probiotics as a supplement to antidepressants in treating MDD. Studies were excluded if they lacked a control group, used probiotics alone, had no full text available, were not original research articles, or were written in languages other than English. The quality of studies was evaluated using Cochrane Risk of Bias 2.0 tools. We performed a meta-analysis using Review Manager v5.4.

Results: Five randomized controlled trials with a total of 369 participants were included. Statistical analysis showed that the pooled standardized mean difference among studies was favourable to the probiotics group (-0.43; 95%CI: -0.71, -0.14) with statistically significant results (p=0.003). Gut microbiota dysbiosis plays a role in the pathogenesis of depression through inflammation and modulation of the hypothalamus-pituitary axis. Probiotics modulate gut microbiota by reducing inflammation and improving the intestinal barrier. In addition, probiotics also improve the metabolism of tryptophan to serotonin and reduce kynurenine accumulation, which is also implicated in depression pathogenesis. The limitation of this study includes the use of varying types and doses of probiotics, which could impact their effectiveness. Additionally, the geographical diversity of the studies, reflecting different genetic and microbial environments, may also affect how individuals respond to probiotic treatment.

Conclusion: In conclusion, probiotics are beneficial for patients with MDD as an adjuvant to antidepressant drugs.

Keywords: adjuvant therapy, antidepressants, depression, probiotics, meta-analysis

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Introduction

Currently, more than 264 million people are still struggling with major depressive disorders (MDD) according to the World Health Organization data. This has put depression as the most common cause of disability worldwide. People with MDD are living with massive distress and dysfunction from daily activities that other healthy people can do.[1] With the ongoing threat from the COVID-19 pandemic, people are forced to face difficult situations, both physically and mentally. There are plethora of internal and external factors as the root causes, from loss of loved ones, changes in daily activities and routine, or even directly from the viral infection.[2,3]

The good news is that most cases of MDD and other mood related disorders are treatable with the right drugs or psychotherapy methods. However, despite the progressive development of dozens of novel antidepressant agents, more than half of all patients treated with antidepressant monotherapy fail to achieve a remission of their depressive episode. This condition is also known as treatment-resistant depression (TRD). Therefore, it is very important to explore a safe well-tolerated, yet effective treatment alternatives that would bring more efficacy on depression remission in patients, not only in TRD patients, but also in common MDD patients.[4,5]

There has been increasing scientists' attention on commensal gut flora effects to the central nervous system (CNS), specifically between the gut flora, the intestine, and the CNS. It suggests that this interaction is recognized as the microbiome-gut-brain axis.[4,5] Therefore, imbalance or disequilibrium state of the gut microbiota may play a vital role on the pathophysiology of many gastrointestinal disease, but more importantly, on CNS disease, including major depressive disorder. Accordingly, regulating the gut microflora balance by daily probiotic intake has a crucial benefit on the function of the brain and prevents the development of several mood-related disorders. Probiotics is found to be a safe and natural way to modulate the gut microbiome by stimulating the growth of some beneficial bacterial species in human intestine.[6–8]

In recent years, there has been a great body of evidence proving the potency of probiotics as adjuvant therapy with antidepressant in alleviating depression, including the treatment-resistant one. By consuming probiotics with current antidepressant drugs, the efficacy of the therapy become much greater, thus, may also increase patients' compliance to the drugs because patients will be satisfied of the improvement they feel after taking the medication.[9] However, to our knowledge, the variety of probiotics species used are very diverse, yet there are still no comprehensive study to compare the efficacy and safety of each of them. Therefore, through our systematic review and meta-analysis, we would like to qualitatively present the comparison of efficacy of each study regarding the use of probiotics as adjuvant vs. placebo, followed by a thorough discussion of its safety profile as a recommendation for clinical use.

Method

This study was conducted according to the Cochrane Handbook 6.2 and the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). Furthermore, this study has been registered to The International Prospective Register of Systematic Review (PROSPERO) according to the regulation for conducting systematic review and meta-analysis (ID: CRD42022379331).

Information sources and search strategy

The search strategy for this systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. Multiple electronic databases, consisting of PubMed, Google Scholar, Cochrane Central Register of Controlled Trials (CENTRAL), EBSCO, CINAHL, and Scopus, were screened by three independent reviewers up to November 18th 2022. The keywords used in the pursuit were customized according to the database used, as shown in Appendix 1. Suitable advanced search techniques were applied whenever appropriate. The literature search was limited by the language, as the authors were only compatible with the English language. Availability of full text articles was also one of the limitation criteria used in the literature searching process. The planned procedure is illustrated in **Figure 1.**

Study eligibility criteria

We applied the following criteria: (1) clinical trial, (2) general population with depression without age and gender limit, (3) received probiotics as adjuvant therapy to antidepressant drugs, and (4) assess outcome in depressive symptoms improvement. The exclusion criteria for our literature search includes: (1) study without control group, (2) study which give

probiotic as sole therapy, (3) studies with irretrievable full text, (4) articles including reviews, commentaries, letters, conference abstracts, and (5) studies written in languages other than English.

Data extraction

We predetermined the outcome sheet in tabular form (MS Excel MS Excel® for Mac; Microsoft Corporation, Redmond, WA, 2018) to include the following data to be extracted: (1) author and year of publication; (2) study characteristics, including study design and location of study; (3) study population, including sample size, severity of depression, mean age, and sex ratio; (4) intervention, type of probiotics used and duration of follow-up; and (5) study outcomes, including comparative indicators, values pre- and post-intervention, as well as significance (p) values. Qualitative characteristics were extracted by two reviewers, and an independent third author rechecked accuracy of extracted data meanwhile performing statistical analysis.

Risk of bias assessment

Quality of each study was accessed using the Cochrane Risk of Bias 2.0 (Cochrane Methods, 2021), which evaluates 5 domains including randomisation bias, bias due to deviations from intended interventions, missing outcome data, outcome measurement, and bias in reporting results. The overall quality of study is then converted based on the Agency for Healthcare Research and Quality (AHRQ) standards. This assessment was performed by three independent reviewers and if there is any disagreement, resolution would be made based on consensus by the three reviewers.

Statistical analysis

We performed statistical analysis using Review Manager ver. 5.4 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen). The mean differences and standard deviations (SDs) were extracted from studies and we interpreted the pooled effects. We utilized the inverse variance, DerSimonian-Laird random effects model as proposed by Riley et al, since we considered that indecipherable heterogeneity could be discovered from studies. Heterogeneity was further evaluated using I^2 statistics, with cut-off limits of 0%, 25%, 50%, and 75% as insignificant, low, moderate, and high heterogeneity, respectively. (Higgins et al., 2003) Additionally, we performed sensitivity analysis following the Duval and Tweedie's trim-and-fill method to identify any outlier study.

Quality of evidence

The quality of evidence was assessed using the GRADE approach. Risk of bias was evaluated using the Cochrane Risk of Bias 2.0 tool. Inconsistency was assessed by assessing the variation in study results. Indirectness was considered if the populations, interventions, and outcomes were directly applicable. Imprecision assessed by examining the width of confidence intervals. Publication bias investigated using funnel plots and statistical tests. Thereby, the study provided high-quality evidence rating for probiotics as adjuvant therapy with antidepressants based on the GRADE criteria.

Result and Discussion

Search results and study selection

Upon database searching, 539 records were identified, after which 171 duplicates were removed. Primary filtering via title and abstract screening removed 290 articles and 38 articles, respectively. Finally, 40 articles are assessed for full-text eligibility. Overall, we found 17 studies with unsuitable design, 5 studies with incomplete outcome data, and 13 irretrievable full-text articles. Final search resulted in 5 eligible studies included in this review. Screening of titles and abstracts of studies was carried out by three independent reviewers. The planned procedure is illustrated in **Figure 1.**

Study characteristics and design

All 5 studies included are finished clinical trials, conducted in several countries including 1 in Russia, 2 in Iran, 1 in Japan, and 1 in the United Kingdom. The dates of publication range from 2018 – 2021, with follow-up durations ranging from 6 weeks – 8 weeks. Among the included studies, participants were mild to moderate depression patients which are diagnosed by certified healthcare workers based on diagnostic statistical manuals for psychiatric disorders. Moreover, participants were randomized into two groups, one that takes a probiotics supplement as adjuvant therapy to common antidepressant drugs and another that takes placebo with antidepressant. Outcomes are measured via parameters including reduction in depression by established mental health questionnaires, both in pre- and post-intervention. The complete characteristics of included studies are shown in **Table 1.**

Study quality assessment

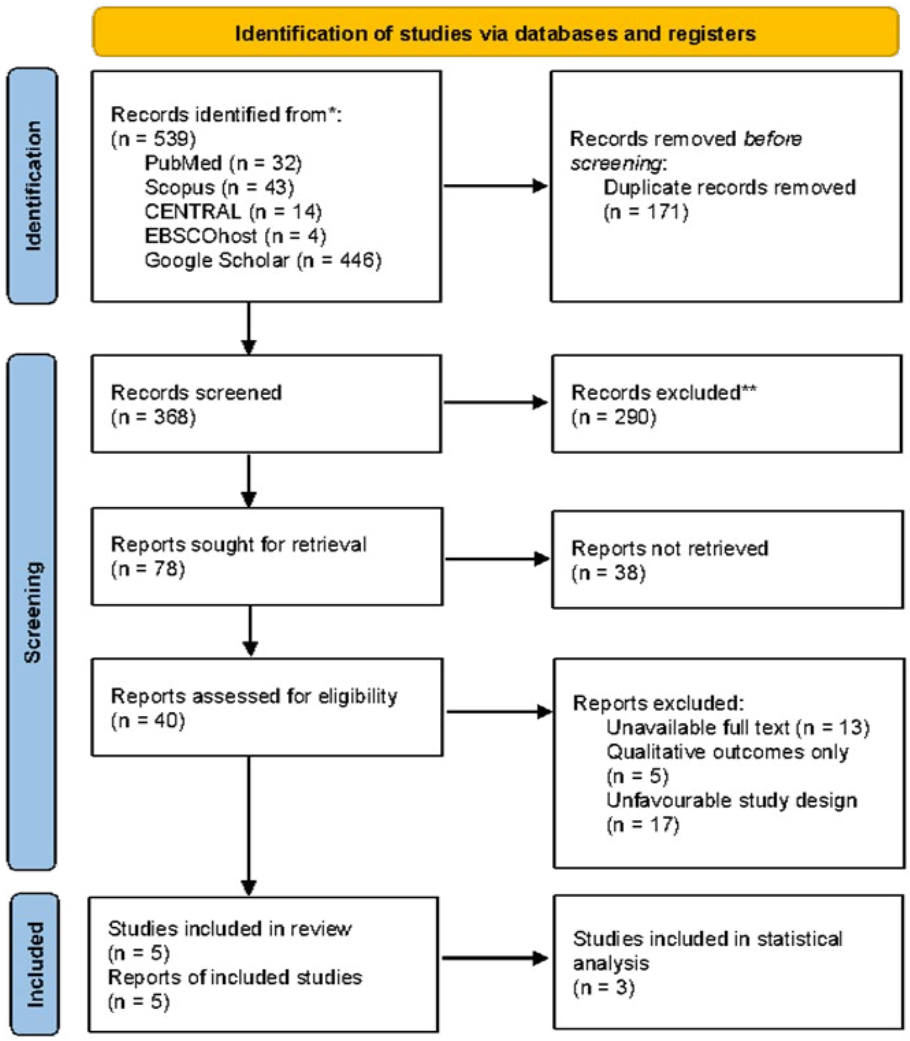

Figure 1. Diagram Flow of Literature Search Strategy

Risk of bias assessment, as shown in **Figure 2** and with the details as shown in Appendix 2, demonstrates that most studies are good quality, except for some concerns in Rudzki et al's study, particularly in the second domain.[21] In this study, the patients were supposed to be aware of their assigned interventions, such that the blinding was not possible. Therefore, there might be a bias due to deviation from the intended interventions. The results of this study have less significant outcomes, and thus can be explained due to the risk of bias during the intervention process.

Efficacy of probiotics for treatment of depression

The included studies assessed the efficacy of probiotics to reduce depressive symptoms in terms of depression quesionnaire's score, especially the Hamilton Depression Rating Scale (HAM-D) and the Beck Depression Inventory (BDI). **Figure 3** depicts the forest plot from 3 studies, namely Ghorbani et al[9], Kazemi et al[10], and Rudzki et al[11]. Statistical analysis showed that the pooled effect estimate of standardized mean difference among studies was favourable to the experimental group (-0.43; 95%CI: -0.71, -0.14) with statistically significant results (p=0.003). Moreover, the overall heterogeneity is negligible (I^2=0%) and therefore sensitivity analysis was not performed. In conclusion, probiotics as adjuvant treatment to antidepressive agents provide better efficacy on alleviating depression compared to placebo.

Probiotics role in depression: a novel therapy

It is estimated that nearly 60% of people with depression worldwide are resistant to pharmacological therapy.[14] In fact, remission after pharmacological treatment occurs in 1 in 3 patients.[15] The pharmacological therapy usually targets the monoamine dysregulation in the brain. Resistance towards pharmacological therapy suggests other factors that may contribute to developing depression in some patients, including the brain-gut

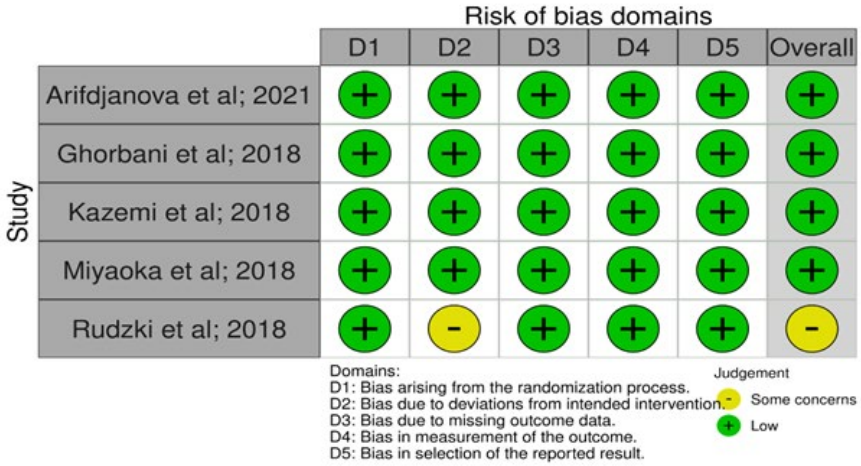

Figure 2. Risk of Bias Assessment

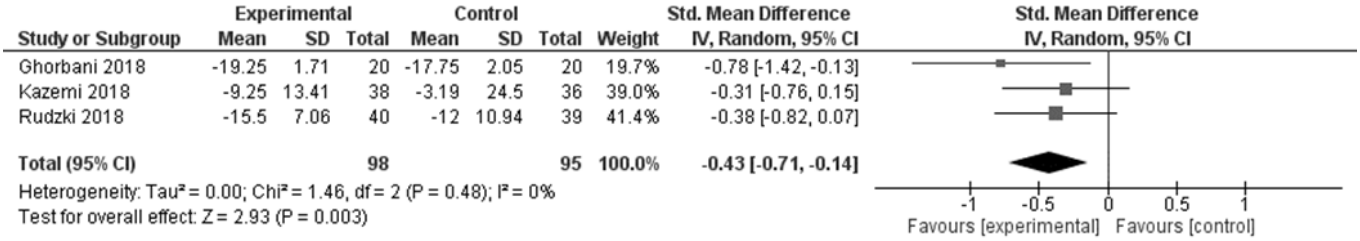

Figure 3. Forest plot of reduction in depressive symptoms post-treatment

axis.[14] Disturbances in the brain-gut axis are associated with alterations in overall behavior and stress-response. Because of that, other therapies have begun to be developed that target the brain-gut axis modulation system.[16]

The role probiotics have in relation to mental health has been extensively studied due to promising effects of microbiota-gut-brain axis (MGBA) modulation to mental health.[17] The gut-brain axis is a network that links the central nervous system and the enteric system, involving endocrine, humoral, metabolic, and immune routes at the same time. Evidence suggests that microbiota of the gut have influences on mental state, emotional regulation, neuromuscular function, and function of the hypothalamus-pituitary axis. In depression, low grade intestinal inflammation is observed, leading to increasing proinflammatory cytokines such as IL-1b, IL-6, TNF-a, and IFN-g. Gut microbiota influence the transcription of these cytokines. In addition, gut microbiota also influence the integrity of tight junctions in enterocytes, so dysbiosis of the gut also affects intestinal permeability, leading to low grade inflammation. Inflammation is thought to play a role in the pathogenesis of depression, in which inflammation alters neurotransmitter metabolism and activates the HPA axis, which affects the availability of neurotransmitter precursors and causes clinical depression.[18]

According to several studies conducted on rats, consumption of probiotics also reduces corticosterone, adrenaline, noradrenaline, and the effect of increasing ACTH due to stress induction, which tend to be high in depressed patients. Probiotics also increase the expression of BDNF or brain-derived neurotrophic factor that functions in plasticity, memory, and neuronal health, which is generally under-expressed in depressed patients. In addition, consumption of probiotics is also known to increase the level of tryptophan (a precursor of serotonin) in plasma, and decrease the level of 5-hydroxyindoleacetic acid or 5-HIAA (the main serotonin's metabolite). This effect is very similar to the mechanism of action of citalopram. Therefore, it can be concluded that the administration of probiotics has a positive impact on the central nervous system's function by regulating important neurotransmitters that contribute to developing depression. In some studies, the use of probiotics also improves memory, reduces anxiety and depressive-like behaviors.[18]

Probiotics as adjuvant therapy

The result of our systematic review is consistent, in which most studies reported significant difference in reduction of depression scores between treatment with adjuvant and control group. Probiotics as adjuvant treatment is especially relevant in treating treatment-

Table 1. Study Characteristics

Studies, year	Location	Sample characteristics					Intervention	
		Sample Definition	Severity	Sample size (n)	Mean Age (y)	Duration	Probiotic (CFU/g)/ Dose	Control; Blinding
Arifdjanova et al[12], 2021	Simferopol, Russia	MDD, DSM-V	Mild to moderate	119	32.9	6 weeks	Bac set forte (multi-probiotic containing ***Lactobacillus*** and ***Bifidobacterium***) + antidepressant (cipralez) Antidepressant: 10 mg/day (90 days),	Placebo + antidepressant; double-blinded
Ghorbani et al[9], 2018	Hamedan, Iran	MDD, DSM-V	Moderate	40	35	6 weeks	Familact (Lactobacillus casaei and L. rhamnosus $3x10^8$ CFU, L. acidofilus $2x10^8$ CFU, L. bulgaricus $2x10^9$ CFU, Bifidobacterium breve $2x10^8$ CFU, B. longum $1x10^0$ CFU, Streptococcus thermophilus $3x10^8$ CFU) Fructoolifosaccharide 100 mg (prebiotic) + antidepressant (fluoxetine)	Placebo + antidepressant; double-blinded
Kazemi, et al[10], 2018	Shiraz, Iran	MDD, ICD-10	Mild to moderate	110	36.47	8 weeks	***L. helveticus*** ROO52, ***B. longum*** R0175 10 x 10^9 CFU (probiotic) or Galactooligosaccharide (prebiotic) + antidepressants (fluoxetine, sertraline, citalopram, or amitriptyline) dose as usual (20-80 mg/day)	Placebo + antidepressants; double-blinded
Miyaoka, et al[13], 2018	Izumo, Japan	TRD, DSM-IV	Moderate	40	44.2	8 weeks	CBM588 60 mg/day + Antidepressants (SNRI or SSRI) dose as usual	Placebo + antidepressants as usual; double-blinded
Rudzki, et al[11], 2018	Scotland, UK	MDD, DSM-IV	Moderate	60	39.13	8 weeks	LP299v $10x10^9$ CFU + antidepressants (SSRI)	Placebo + antidepressants; double-blinded

*Abbreviations: NR = Not reported; MDD: major depressive disorder; DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CFU: colony forming unit; TRD: treatment-resistant depression; SSRI: selective serotonin reuptake inhibitor; SNRI: selective norepinephrine reuptake inhibitor.

Table 2. Summary of study outcomes

Studies; year	Outcome Parameter	Value with Intervention		Value without intervention		Significance (p-value)	Adverse events
		Value at baseline (SD)	Value post-treatment (SD)	Value at baseline (SD)	Value post-treatment (SD)		
Arifdjanova et al[12], 2021	HAMD-17	12.4±4.6	declined 56%	11.9±4.9	declined 44%	0.083	Not reported
Ghorbani et al[9], 2018	HAM-D	22.90 (22.08 - 23.72)	3.65 (2.92 - 4.38)	22.55 (21.80 - 23.30)	4.80 (4.16 - 5.44)	0.013*	Bloating and nausea (20%). Diarrhea (10%). Abdominal cramp (15%). Difference were not significant between intervention and placebo group
Kazemi, et al[10], 2018	BDI Scale	18.25 (14.15 - 21.62) SE: 1.90	9.0 (7.43 – 14.12) SE: 1.70	18.74 (14.11 - 23.13) SE: 3.92	15.55 (11.36 - 21.26 SE: 2.52	0.042*	Gastrointestinal complaints, nausea, fever, body aches, increased appetite.
Miyaoka, et al[13], 2018	HAMD-17	31.9 (2.8)	declined >50%	31.8 (4.0)	NR	0.001*	Mild, transient headache. Difference were not significant between intervention and placebo group
	BDI Scale	43.8 (4.3)	declined >50%	41.4 (4.8)	NR	0.001*	
	BAI Scale	32.8 (5.8)	declined >50%	33.3 (4.7)	NR	0.001*	
Rudzki, et al[11], 2018	HAMD-17	21.53 (6.03)	6.03 (3.68)	22.00 (7.92)	10.00 (7.54)	0.205	Gastrointestinal complaints, headache, palpitations. Difference were not significant between intervention and placebo group
	SCL-90	2.41 (0.64)	1.1 (0.73)	2.67 (0.64)	1.56 (0.92)	0.684	
	PSS-10	28.27 (4.91)	14.86 (6.47)	29.70 (3.95)	19.23 (8.24)	0.214	

NR = Not reported; SD: standard deviation; SE: standard error; HAM-D: Hamilton Depression Rating Scale; HAMD-17: Hamilton Depression Rating Scale 17 item; BDI: Beck's Depression Inventory ; BAI: Beck's Anxiety Inventory; SCL-90: Symptom checklist 90; PSS-10: Perceived stress scale.

resistant depression (TRD), with study by Miyaoka et al reporting 70% of TRD patients responding to treatment and a remission rate of 35%[13]. On the other hand, prebiotics also cause greater reduction in depression scores, but this result is not significant. Therefore, probiotics remains the more superior method of treatment compared to probiotic.[10]

In addition to depression scores, supplemental probiotics also have positive effects on other parameters. Study by Kazemi et al showed that probiotics also reduces serum kynurenine/tryptophan ratio. Tryptophan is metabolized into serotonin, so shunting of tryptophan to the kynurenine pathway can cause serotonin deficiency, which leads to depression. Here, probiotics play a role in reducing the enzymes responsible for converting tryptophan to kynurenine, therefore driving tryptophan along the serotonin pathway.[10]

Another mechanism is that probiotics affect the synthesis of enzymatic cofactors in kynurenine metabolism towards NAD+ and ATP synthesis, such as vitamin B2 and B6. Inflammation and stress is related to accumulation of kynurenine, so this may be another benefit of probiotics in reducing inflammation.[11] Another study by Akkasheh et al also showed that supplemental probiotics decreases serum hs-CRP levels, a biomarker of systemic inflammation. Probiotics increase the production of short chain fatty acids (SCFA) and decrease the expression of Il-6, therefore playing a role in reducing inflammation.[5]

Arifdjanova et al also found that supplemental probiotics provided a more pronounced effect in limiting stress response.[12] Elevated cortisol is a physiological biomarker for emotional disorders, including depression. Along with noradrenaline and adrenaline, these hormones activate the hypothalamus-pituitary-adrenal axis (HPAA), which causes hyperactivity of the sympathetic system. This is a key in the development of depression. Increasing adrenaline and noradrenaline also increase the growth of Bacteroides and other opportunistic gut bacteria, leading to a vicious cycle of increasing production of catecholamines. The use of probiotics decreases HPAA activity, therefore correcting inadequate stress response.[12]

Various probiotics are shown to benefit major depressive disorder. Lactobacillus and Bifidobacteria are often used as evidence suggests they inhibit growth of pathogenic bacteria and fungi, improve intestinal barrier, enhance synthesis of SCFA, and modulates inflammatory cytokines.[11] Studies showed that L. rhamnosus and L. helveticus have positive effects on intestinal barriers following psychological stress, and combination with Bifidobacterium longum resulted in improvement in mental health.[5,10,11] L. plantarum were shown to also significantly influence kynurenine concentration and metabolism in depressed patients. However, it does not improve depression score parameters significantly.[11] Others such as L. acidophilus, L. casei, and B. animalis were also shown to improve depression parameters and reduce inflammation.[5,18]

Clostridium butyricum (CBM588) was also used and provided antiinflammatory and neuroprotective effects, including neurogenesis, antioxidation, and anti-glutamate excitotoxicity.[13] Based on studies included in this systematic review, combination of probiotics seems to have better results in significantly reducing depression scores, compared to single type probiotics such as in Rudzki et al's study.[11] Several fixed dose combination is available, such as the Bac set forte and Familact, as well as yogurts and capsules containing multiple probiotics.[9,12] There is no consensus on the amount of probiotics needed to improve depression as an adjuvant therapy, but in general, a minimum amount of 109 CFU has been recommended to yield health benefits.[17]

Studies cited in our systematic review reported minimal adverse effects, good tolerability, and good compliance. No significant difference in adverse effects were reported between placebo and probiotic group.[5,9–11] Some of the most common side effects were gastrointestinal complaints such as bloating, nausea, or cramps. Neurological effects such as headache and tremor, fever, and increased in appetite were also reported.[9–11] Interestingly, Rudzki et al's study showed that gastrointestinal complaints were seen only on patients using SSRI as antidepressant, so it is likely that SSRI also contributed to that side effect.[11]

Drugs interaction: probiotic and SSRI

Until now, there has been no definite statement that can describe the microbiome-drug interaction, hence the interaction between probiotics and SSRIs cannot be described with certainty. However, it has been suggested that some SSRI drugs can affect the balance and integrity of the gut microbiome, so that the side effects and therapeutic effects of these drugs can be altered. This is also thought to explain why some patients require higher doses than others even though it does not result in a significant increase in SERT binding.[19]

In addition, various types of probiotics and SSRIs also provide different interaction mechanisms, which have not been fully studied and still cannot be ascertained. Abdrabou A, et al conducted a study on rats by giving Citalopram (SSRI) and Lactobacillus showed that the concurrent administration of Lactobacillus and Citalopram had a positive effect on depressive symptoms. It was stated that Lactobacillus was able to lower kynurenine levels in brain tissue, which cannot be done by taking citalopram alone. In addition, the study also showed that mice given citalopram and Lactobacillus showed a better effect than those given Citalopram or Lactobacillus alone.[20]

Strengths and limitations

This study is the first systematic review that explores the efficacy and safety of probiotics as adjuvant in depression therapy. Studies included in our review uses a variety of antidepressants including SSRI, SNRI, and tricyclic antidepressant, therefore the difference of effect due to different antidepressants is minimized and the result of this study may be generalized across all depressed patients using antidepressants. The use of probiotics as an adjuvant may also be beneficial in reducing the amount of antidepressants used, therefore reducing side effects from antidepressants, and also as an alternative for treatment-resistant depression before undergoing more aggressive and invasive treatment.

This study is not without limitations. First, the probiotics selected in the studies cited are not the same, with different doses and different combinations of probiotics, therefore this may have affected the results. Second, studies are located in different countries, where genetics and microbial exposure may influence individual response to probiotics.

Conclusion

This review focuses on the use of probiotics as adjuvant therapy in depressed patients. It can be said that probiotics have the potential to enhance therapeutic effects in patients with depression who are taking antidepressant drugs. Probiotics alone are known to have positive effects on the central nervous system such as anti inflammatory, reduces stress hormones (adrenaline, noradrenaline, corticosterone, and ACTH due to stress induction), increase the expression of BDNF which has neuroprotective effect, increase the level of tryptophan, and decrease the level of 5-HIAA due to the brain-gut axis.

However, using probiotics alone or antidepressant drugs alone does not give a significant effect on treating depression, even though probiotics have their own potential health benefits. Several studies have shown that given probiotics with antidepressant drugs improves overall patient's depressive symptoms and gives significant difference in reduction of depression scores between control group and treatment with adjuvant, especially in TRD patients. Because of that, further research is recommended because of the variability in gut microbiome in each country. In addition, further research is also needed regarding the appropriate dose given to patients.

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Conflict of Interest

The authors declare no competing interests/conflict of interests in the making of this manuscript.

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Supplementary Files

Probiotics as adjuvant therapy with antidepressants vs placebo to treat major depressive disorder: a systematic review and meta-analysis of randomized controlled trials

Appendix 1. Table of keywords used in literature search

Database	Keywords	Hits
PubMed	(("Depressive Disorder, Major"[Mesh]) OR "Depression"[Mesh]) AND (probiotics OR "probiotics"[MeSH Terms] OR probiotic[Text Word] OR probiotics prophylaxis) AND (adjuvant OR combination therapy OR adjunctive therapy OR "adjuvants, pharmaceutic"[All Fields] OR "adjuvants, immunologic"[All Fields] OR "adjuvants, pharmaceutic"[MeSH Terms] OR "adjuvants, immunologic"[MeSH Terms] OR adjuvant[Text Word])	32
Scopus	TITLE-ABS-KEY ((probiotics OR prebiotics) AND (depression OR depressive AND disorder OR mdd OR "major depressive disorder" OR "treatment-resistant depression") AND (adjuvant OR adjunctive OR combination)) AND (LIMIT-TO (PUBSTAGE, "final")) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (LANGUAGE , "English"))	43
CENTRAL	(Major depressive disorder or mdd or major depression) AND (probiotics or probiotic therapy or probiotic prophylaxis) AND (adjuvant therapy OR adjuvant OR adjunctive) AND (placebo or placebo effect or nocebo or placebos)	14
EBSCOhost	(Major depressive disorder or mdd or major depression) AND (probiotics or probiotic therapy or probiotic prophylaxis) AND (adjuvant therapy OR adjuvant OR adjunctive) AND (placebo or placebo effect or nocebo or placebos)	4
Google Scholar	(Major depressive disorder or mdd or major depression) AND (probiotics or probiotic therapy or probiotic prophylaxis) AND (adjuvant therapy OR adjuvant OR adjunctive) AND (placebo or placebo effect or nocebo or placebos)	446

Appendix 2. Cochrane risk of bias tools 2.0

Domain 1: Risk of bias arising from the randomization process

Signaling questions	Response options	Arifdjanova et al, 2021	Ghorbani et al, 2018	Kazemi et al, 2018	Miyaoka et al, 2018	Rudzki et al, 2018
1.1 Was the allocation sequence random?	Y / PY / PN / N / NI	Y	Y	Y	Y	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y / PY / PN / N / NI	Y	Y	Y	Y	Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Y / PY / PN / N / NI	N	N	N	N	N
Risk-of-bias judgement	Low / High / Some concerns	Low	Low	Low	Low	Low

Abbreviations: Y: Yes; PY: Probably yes; PN: Probably no; N: No; NI: No information

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Signaling questions	Response options	Arifdjanova et al, 2021	Ghorbani et al, 2018	Kazemi et al, 2018	Miyaoka et al, 2018	Rudzki et al, 2018
2.1. Were participants aware of their assigned intervention during the trial?	Y / PY / PN / N/ NI	N	N	N	N	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y / PY / PN / N/ NI	N	N	N	N	N
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	NA / Y / PY / PN / N / NI	NA	NA	NA	NA	NA
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	NA / Y / PY / PN / N / NI	PN	N	N	N	NA
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	NA / Y / PY / PN / N / NI	PN	N	N	N	PY
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA / Y / PY / PN / N / NI	Y	Y	Y	Y	Y
Risk-of-bias judgement	Low / High / Some concern	Low	Low	Low	Low	Some concerns

Abbreviations: Y: Yes; PY: Probably yes; PN: Probably no; N: No; NI: No information

Domain 3: Missing outcome data

Signaling questions	Response options	Arifdjanova et al, 2021	Ghorbani et al, 2018	Kazemi et al, 2018	Miyaoka et al, 2018	Rudzki et al, 2018
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y / PY / PN / N / NI	Y	Y	Y	Y	Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA / Y / PY / PN / N	NA	NA	NA	NA	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA / Y / PY / PN / N / NI	NA	NA	NA	NA	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA / Y / PY / PN / N / NI	NA	NA	NA	NA	NA
Risk-of-bias judgement	Low / High / Some concerns	Low	Low	Low	Low	Low

Abbreviations: Y: Yes; PY: Probably yes; PN: Probably no; N: No; NI: No information

Domain 4: Risk of bias in measurement of the outcome

Signaling questions	Response options	Arifdjanova et al, 2021	Ghorbani et al, 2018	Kazemi et al, 2018	Miyaoka et al, 2018	Rudzki et al, 2018
4.1 Was the method of measuring the outcome inappropriate?	Y / PY / PN / N / NI	N	N	N	N	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Y / PY / PN / N / NI	N	N	N	N	N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	NA / Y / PY / PN / N / NI	N	N	N	N	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA / Y / PY / PN / N / NI	NA	NA	NA	NA	NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA / Y / PY / PN / N / NI	NA	NA	NA	NA	NA
Risk-of-bias judgement	Low / High / Some concerns	Low	Low	Low	Low	Low

Abbreviations: Y: Yes; PY: Probably yes; PN: Probably no; N: No; NI: No information

Domain 5: Risk of bias in selection of the reported result

Signaling questions	Response options	Arifdjanova et al, 2021	Ghorbani et al, 2018	Kazemi et al, 2018	Miyaoka et al, 2018	Rudzki et al, 2018
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y / PY / PN / N / NI	Y	Y	Y	Y	Y
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...						
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Y / PY / PN / N / NI	N	PN	N	N	N
5.3 ... multiple eligible analyses of the data?	Y / PY / PN / N / NI	N	N	N	N	N
Risk-of-bias judgement	Low / High / Some concerns	Low	Low	Low	Low	Low

Abbreviations: Y: Yes; PY: Probably yes; PN: Probably no; N: No; NI: No information