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Review

Association of Gut-Microbiome and mental health and effects of probiotics on psychiatric disorders: A Meta-analysis and systematic review

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Abstract

Background: A correlation between gut microbiome and mental health has drawn significant attention lately. The effects of microbiome microorganisms and their byproducts on disease states represent a complex and dynamic field of study. The objective of this article is to review the association of gut microbes and mental health and the effects of probiotics on psychiatric disorders, if any.
Methodology: This meta-analysis was conducted using the PRISMA standards. We have compiled the most recent advancements in the field according to human research published in this Systematic review and meta-analysis.
Results: The forest plot analysis revealed that probiotics or probiotics combined with other intervention modalities did significantly reduce some extent of mental disorders in comparison to the control group (Standardized mean difference) SMD = 0.95, 95% Confidence Interval (CI): −6.52 to 8.42, P value< 0.01.
Conclusion: Overall, the reviewed literature supports the importance of gut microbiota–brain interaction in human mental illnesses, including the impact of probiotics on mental health outcomes and brain connection.

Keywords: Anxiety; Bacteria; Depression; Gut-microbiome; Mental Health.

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Quick Response Code:

Introduction

The importance of the gut microbiome in human wellness and illness and evidence linking it to the development of chronic diseases has made it a major area of study during the past ten years [1]. The effects of microbiome microorganisms and their byproducts on disease states represent a complex and dynamic field of study. Although not all disease pathways are fully understood, some general principles may be defined, such as the connection between immunological dysregulation and dysbiosis. An imbalance in the microbiome's composition, known as dysbiosis, is marked by the overrepresentation of some microbes and the under representation of others.

Immune dysregulation, or the inability of the immune system to distinguish between benign germs and harmful infections, can be caused by this imbalance. This imbalance may be a factor in chronic inflammation, a defining feature of many diseases, including autoimmune disorders. Molecular mimicry, in which some bacteria or their constituents have structural similarities with host tissues, is another important mechanism. Because similar chemicals are present in infections, the immune system mistakenly targets its tissues. It is thought that this process is essential for treating autoimmune illnesses [2].

Additionally, there is a correlation between the gut microbiome and mental health, which has recently drawn significant amounts of attention [3-7]. The vagus nerve, microbial regulation of neuroimmune signaling, tryptophan metabolism mediated by the gut microbiota, microbial control of neuroendocrine function, and microbial synthesis of neuroactive compounds are just a few examples of how the gut microbiota has been suggested to have an impact on the brain and mental health [8,9]. Additionally, neurotransmitters such as glutamate, dopamine, and serotonin, which are crucial for neurological and immunological processes in the brain, may be produced and regulated by the gut microbiota [10].

The seminal research conducted by Sudo and colleagues, which revealed that germ-free mice had a compromised stress response, put forth the theory of the gut-brain axis. This existence and the hypothesis that the gut-brain axis (GBA) goes beyond these two pathways, into the endocrine, neurological, and immunological pathways, were also corroborated by additional research employing germ-free mice [11,12].

Animal research provides a large portion of the information on gut microbiota-brain axis interactions and mental health consequences [13]. We have compiled the most recent advancements in the field according to human research published in this systematic review and meta-analysis. This study has two sections which are its main objectives too. In one section, we have shown that gut microbiota and mental health are related, and in the other, we have used a forest plot to determine the impact of probiotics on mental wellness.

Methodology

This study is registered under the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42024520373. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards were used to conduct this meta-analysis [14]. Since all the studies were predicated on previously published research, neither ethical clearance nor written consent was necessary. The PRISMA checklist is attached to the appendix/supplementary file.

Eligibility criteria:

The Population, Intervention, Comparison, Outcomes, and Study (PICOS) guidelines require that an original study meets certain eligibility standards for inclusion in our meta-analysis [15].

Study types:
Observational and experimental studies.

Participant types:

Inclusion Criteria:
The included studies met the following requirements. First, research on the relationship between gut microbiota and mental health conditions such as anxiety, depression, bipolar disorder, schizophrenia, autism spectrum disorder (ASD), and eating disorders that evaluated and documented empirical data (primary or secondary). Second, the kinds of study designs that can be done are restricted to cross-sectional, case-control, cohort, and randomized control trials. Third, studies with only human participants were included in this review article. Fourth, studies where validated self-report screening tools, structured interviews, or other diagnostic criteria were used to confirm the presence of anxiety, depression, bipolar disorder, eating disorders, and autism spectrum disorder (ASD).

Exclusion Criteria:
The following were the exclusion criteria: (1) Research such as commentary, letters to the editor, brief communications, and reviews of the literature. (2) Research that neglects or fails to disclose the instruments used to establish the presence of mental health issues. (3) Research works that have not been written in the English language.

Interventions:
Probiotics were administered to the experimental class, while a placebo was given to the control group.

Outcomes:
Several measures were used in all included trials to assess the impact of probiotics, including the ADAS-cog (Alzheimer's Disease Assessment Scale-Cognitive subscale) total score to assess cognitive function, the MMSE (Mini Mental Status Exam) total score, the HAM-A (Hamilton Anxiety) Rating Scale for anxiety, and Beck's Depression Inventory-II for depression.

Search strategy:
The search was restricted to human studies and contained the following search terms: (gut-microbiome* OR bacteria) and (anxiety) and (depression), and (bipolar disease), and (autism spectrum disorder), and (schizophrenia), and (eating disorders).

On December 23, 2023, a preliminary search was carried out without any limitations regarding the publication date on the ISI (Institute for Scientific Information) Web of Science and PubMed databases. A follow-up Google Scholar search was conducted to find any studies that might have been overlooked. Examining the bibliographies of pertinent publications and current reviews served as an additional supplement to this. BG and RG separately assessed each search result considering the search criteria, and VS arbitrated any disagreements. BG and RG carried out the data extraction of the fundamental study features, effects of treatment, tolerability measurements, and quality assessment, and BG analyzed the results.

Literature selection:
The search technique was executed by BG and RG, who also obtained the abstracts of relevant papers. After that, duplicate publications were removed, and all the publications were imported into the program Endnote X9. Upon reviewing the abstracts, full texts, and titles of the articles, we separately identified the publications that met the inclusion and exclusion criteria. When BG and RG could not agree on what

research to include or eliminate, they provided information to another researcher (AM, VS) to resolve the issue.

Data extraction:
The data were extracted from the research and included individually by BG and RG. We extracted and cross-checked the protocol characteristics (type of study, population type, etc.), first author, publication year, and country of origin, as well as the research variables (DNA sequencing technique, type of psychiatric disease, etc.). Any contradictory data were checked with another researcher (AM, VS).

Risk of bias assessment:
Based on the Cochrane risk of bias (RoB) approach, two researchers assessed each included publication's methodological quality. Evaluations were conducted in the following domains: performance bias (blinding of participants and staff), reporting bias (selective reporting), random sequence generation and allocation concealment, attrition prejudice (incomplete outcome data), and detecting bias (blinding of outcome evaluation) [16]. The three outcomes—low risk, high risk, and unclear—were evaluated [17]. Furthermore, the differences were resolved through internal group discussions and by contacting the authors to clarify the details with a third-party arbitrator.

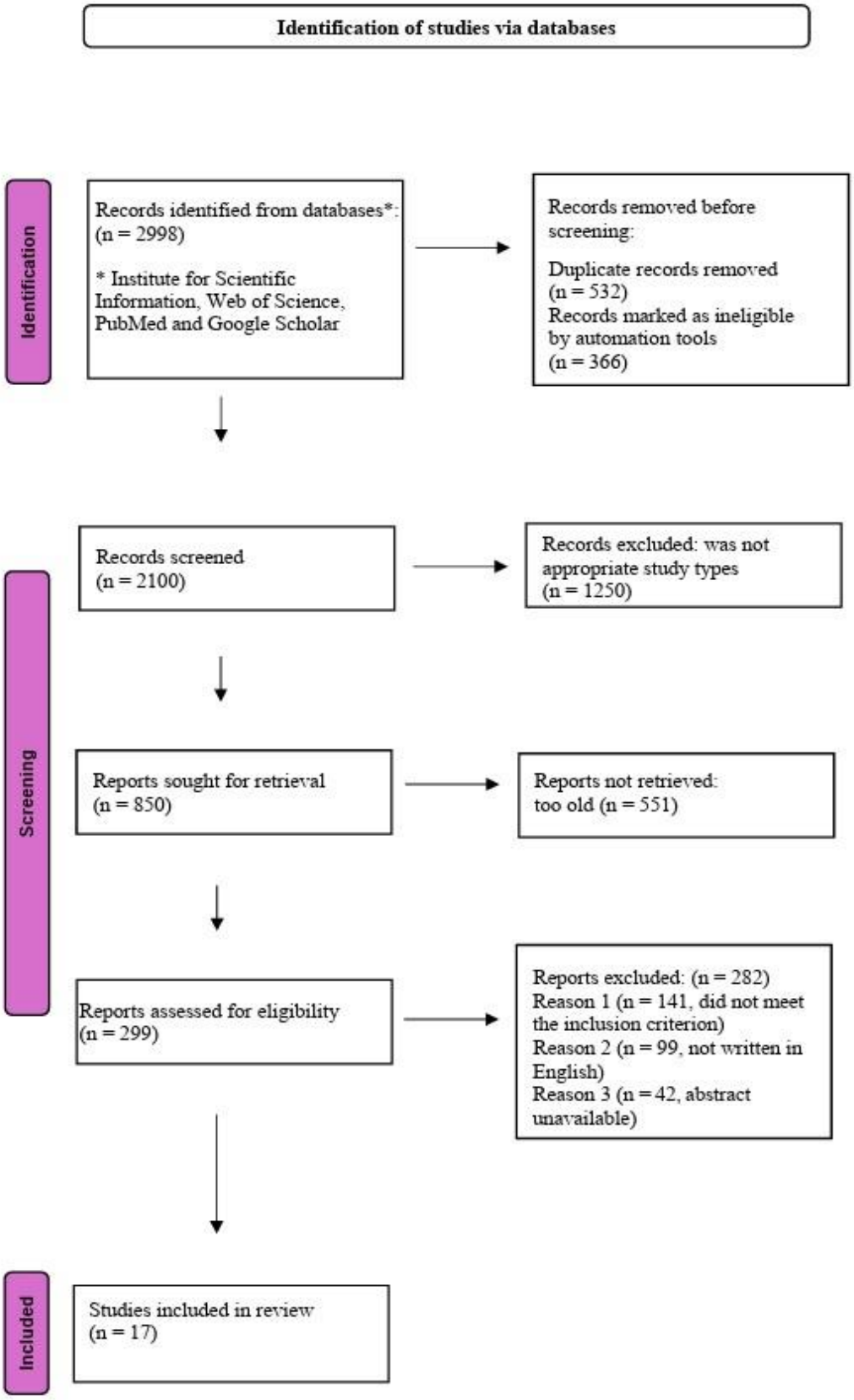
Level of evidence:
We applied the GRADE technique to assess the overall quality of the evidence [18]. The five factors that define the value of the evidence include study limitations, indirectness of the proof, inexplicable heterogeneity or conflict of outcomes, inaccuracy of results, and a high likelihood of publication bias [19]. The GRADEpro or GRADEpro GDT (Guideline Development Tool) site (www.gradepro.org) provided the data table summary [20]. Two researchers (BG and RG) independently assessed the quality of the proof and the RoB. The choice was made after the addition of an additional researcher (AM).

Statistical analysis:
The statistical analysis was performed using R software. The evaluation of continuous outcomes was performed by calculating the standard mean deviation (SMD) with a 95% confidence interval (CI), which allowed trials that assessed the same result using multiple scales to be combined. To reduce the number of comparisons, we merged the experimental or control groups if the study contained many experimental groups. For trials with little or little heterogeneity ($P \geq 0.1$ or $I2 \leq 50\%$), a fixed-effects model was utilized; for studies with considerable heterogeneity ($P < 0.1$ or $I2 > 50\%$), a random-effects model was applied. Using a funnel plot analysis, the possibility of publication bias was assessed for a meta-analysis.

Results

Literature selection:
There were 2998 publications found in all. A total of 2100 articles remained after duplicates were removed. After reviewing the title pages and abstracts, and removing reviews and other unrelated studies, only 17 papers remained. Ultimately, an evaluation of 10 out of the 17 papers was conducted to determine whether the gut microbiota and mental health were related (Table 1) [21-30]. The final meta-analysis to determine the impact of probiotics on psychological disorders included the remaining 7 papers [31-37]. The whole flow of the study scanning procedure is shown in Figure 1.

Figure 1: PRISMA flow diagram.



Characteristics of the included studies:

Seventeen studies including people with mental health issues were included in our research. Probiotics or traditional therapy enhanced with probiotics was given to the experimental group, whereas conventional treatment was given to the control group. Table 1 summarizes the key elements of the included studies that looked for a connection between the gut microbiota and mental health.

Table 1: Characteristics of Sample Studies

Author, year, country	Type of Study and Population	Sequencing	Psychiatric Disorder	Findings of the study
Pan Q et al., 2021, China [21]	The observational study, Elderly	r 16S ribosomal RNA (rRNA) quantitative arrays and bioinformatics analysis.	Alzheimer's disease	Samples from the MCI (mild cognitive impairment) group showed a substantial increase (Staphylococcus intermedius) or decrease (Bacteroides salyersiae) in several bacterial species.
Ling Z et al., 2022, China [22]	Observational study, Elderly	16S rRNA gene by MiSeq sequencing	Schizophrenia (SZ)	The compositional changes in SZ-associated bacteria, such as Faecalibacterium, Roseburia, Actinomyces, Butyricicoccus, and Prevotella, were detected using the Linear Discriminant Analysis Effect Size (LEfSe).
Sheng C et al, 2021[23]	Observational study, Elderly	16S ribosomal RNA (rRNA) Illumina Miseq sequencing technique.	Alzheimer's disease	There was a trend towards a steady drop in the abundance of the phylum Firmicutes, class Clostridia, order Clostridiales, family Ruminococcaceae, and genus Faecalibacterium from NC (normal control) to SCD (subjective cognitive decline) and CI (cognitive impairment). More specifically, when compared to NC, the anti-inflammatory genus Faecalibacterium was substantially less abundant in SCD. Furthermore, there was a correlation between the three groups that changed bacterial taxonomy and cognitive function.
Ling Z et al.,2022, China [24]	Case-control study, school-aged children	16S rRNA gene sequencing	Depression	In the depressed group, there was an enrichment of pro-inflammatory genera such Streptococcus and a reduction of anti-inflammatory genera like Faecalibacterium. These modifications correlate with modified bacterial functions, particularly metabolite synthesis that modulates immune response. Additionally, we found that children with depression had a decreased amount of anti-inflammatory cytokines like IFN-γ (interferon) and greater amounts of pro-inflammatory cytokines like IL-17 (interleukin).
Ma B et al., 2019, China [25]	Observational study, Children with Autism Spectrum Disorder (ASD) 6-9 years of age	16S rRNA gene sequencing	Autism Spectrum Disorder	In comparison to healthy controls, kids who had ASD had a reduced proportion of Acidaminococcaceae in their families. Furthermore, the ASD group showed a decline in the relative abundance of the taxa Lachnoclostridium, Flavonifractor, Tyzzerella subgroup 4, and unidentified Lachnospiraceae.

Wang L et al.,2023, China [26]	Observational study, children	16S rRNA gene sequencing	Attention Deficit Hyperactive Disorder (ADHD)	According to IVW (inverse variance weighted) results, the following genera were linked to a lower risk of ADHD: genus Butyricicoccus (p = 0.009), genus Roseburia (p = 0.009), genus Desulfovibrio (p = 0.015), genus LachnospiraceaeNC2004group (p = 0.026), genus Romboutsia (p = 0.028), and family Oxalobacteraceae (p = 0.048). These results were corroborated by IVW data.
Domènech L et al.,2022, Spain [27]	Observational study, adults with a mean age of 40.16 years	16S rRNA gene sequencing	Obsessive Compulsive Disorder (OCD)	The OCD stool samples revealed a tendency towards reduced α-diversity in bacteria, along with a rise in the overall abundance of Rikenellaceae, especially in the species Alistipes, and a decrease in the comparative abundance of Prevotellaceae, Agathobacer, and Coprococcus, two genera belonging to the Lachnospiraceae.
Park M et al., 2020, Korea [28]	Randomized Control Trial, adults between 20-30 yrs	Polymerase Chain Reaction	Depression	We found that the Lachnospiraceae family (Lachnospiraceae_uc and Murimonas) and brain-derived neurotrophic factor (BDNF) positively correlated with depression.
Zhu R et al., 2023, China [29]	Randomized Control Trial, college students	16S rRNA gene sequencing	Anxiety	According to the findings, college students who are test-anxious may find that using L. plantarum JYLP-326 as an intervention is a useful way to reduce their anxiety, sadness, and insomnia. This effect's possible mechanism may have to do with controlling faecal metabolites and gut bacteria.
Tanaka A et al., 2023, Japan [30]	Observational study, adults	16S rRNA gene sequencing	Insomnia, Depression, Anxiety	Following the false discovery rate (FDR) adjustment, the insomnia group displayed less alpha diversity in the Chao1 and Shannon indices compared to the non-insomnia group. In the non-insomnia group, there was a positive correlation between the PSQI (Pittsburg Sleep Quality Index) scores and the proportion of individuals of the species Bacteroides. According to our research, some taxa may have an impact on how well people with anxiety and depression sleep.

Risks of bias and the level of evidence:

Based on the assessment criteria, we found moderate quality evidence supporting the potential use of probiotics in the treatment of mental health issues. We found that the likelihood of uncertainty bias and the small number of included individuals had a detrimental effect on the dependability of the evidence. Evidence of a moderately high caliber of probiotics suggested that probiotics may decrease mental health illnesses. The risk of bias in the included studies is shown in Figures 2& 3 below.

Figure 2: Risk of Bias in the included studies

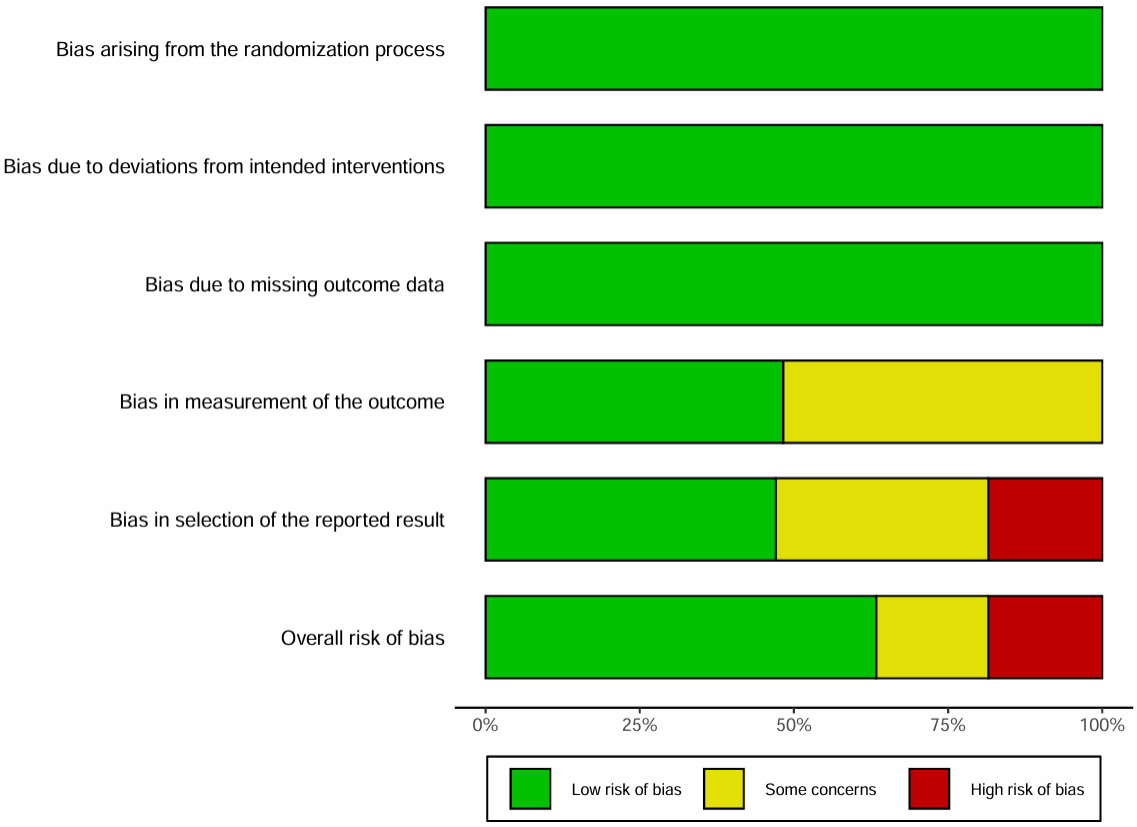
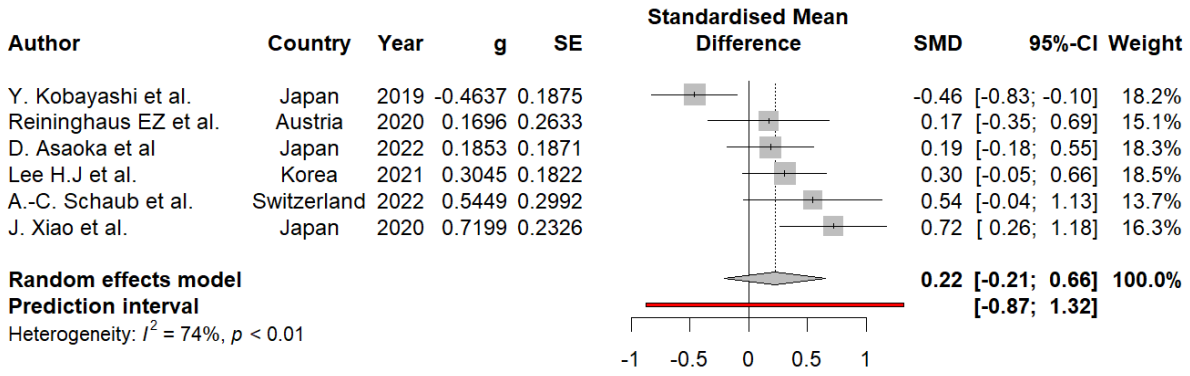


Figure 3: Traffic light plot of Risk of Bias in the included studies

Meta-analysis:

To investigate the efficacy of probiotics in treating mental health disorders, forest plot analysis revealed that probiotics alone or probiotics combined with other intervention modalities significantly reduced mental disorders to some extent in comparison to those in the control group (SMD = 0.95, 95% CI: −6.52 to 8.42, P < 0.01) (Figure 4). The heterogeneity among the randomized control trials included in the meta-analysis was found to be 74%.

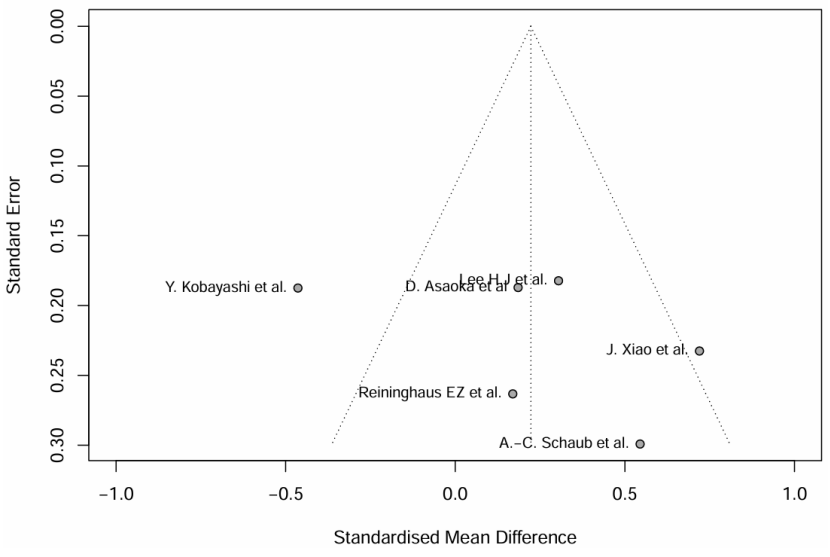
Figure 4: Forest plot of Depression in the two groups of patients. Confidence Interval (CI), Standard Error (SE), Standard Mean Difference (SMD)



Publication bias:

Funnel plots were made for every observation index. The funnel plots demonstrate the generally symmetric and targeted nature of the included research, suggesting little to no evidence of publication bias.

Figure 5. Funnel chart of depression scale of the two groups of patients, one receiving probiotic and the other not receiving the same.



Discussion

Probiotics may help reduce stress, anxiety, depression symptoms, and other mental health issues, according to data from healthy volunteer studies. This review also revealed that probiotics aid in enhancing human cognitive performance. All studies showed high levels of tolerance and adherence to the intervention.

Probiotics preserved microbial diversity and boosted the abundance of the Lactobacillus genus. Schaub AC et al. demonstrated the efficacy of probiotics in increasing the abundance of particular taxa. In the probiotics group, a decrease in depression symptoms was linked to an increase in Lactobacillus. After the probiotic intervention, there was a significant decrease in putamen activation in response to neutral faces. In addition to improving modifications to the gut microbiota and brain, an add-on probiotic treatment reduces depressive symptoms. This suggests that the MGB (microbiota-gut brain) axis plays a role in major depressive disorder and highlights the possible benefits of microbiota-related treatments as practical, affordable, and non-stigmatizing therapies [31].

The findings of the Y. Kobayashi et al. study point to the risk associated with B. breve A1 intake as well as its ability to preserve cognitive function in senior patients who have memory problems [32]. According to comparable findings by J. Xiao et al., B. breve A1 is a secure and efficient method for enhancing memory skills in individuals who may be mildly cognitively impaired [33]. In their investigation, D. Asaoka et al. discovered that taking probiotics for 24 weeks slowed the progression of brain atrophy, indicating that B. breve MCC1274 may help MCI patients avoid cognitive impairment [34].

The results of the study by Y. Kobayashi et al. demonstrated that oral B. breve A1 supplementation enhanced cognitive function in participants with MCI (mild cognitive impairment), indicating the possible benefits of B. breve A1 for enhancing cognitive function and preserving elderly people's quality of life [35]. In a study by Reininghaus EZ et al., four weeks of probiotics combined with biotin supplementation demonstrated an overall positive effect on the treatment of inpatients diagnosed with major depressive disorder. However, the microbial diversity profile was the only difference between the probiotic intervention group and the placebo group; clinical outcome indicators were unchanged [36].

Compared with the placebo group, the probiotic NVP-1704 group utilized by Lee H.J et al. experienced a more notable reduction in anxiety symptoms at four weeks and depression symptoms at eight weeks of treatment. The quality of their sleep also improved for thxsose on NVP-1704. Their serum interleukin-6 levels decreased because of NVP-1704 therapy. Additionally, NVP-1704 altered the makeup of the gut microbiota by increasing Bifido bacteriaceae and Lactobacillaceae while decreasing Enterobacteriaceae [37].

Limitations:

An absence of power in these investigations may have prevented the meta-analysis from reaching statistical significance, resulting in a false-negative result. The fact that only seven papers satisfied our inclusion requirements for the meta-analysis suggests that the body of evidence is still insufficient. Synonyms of the keywords were not included in the search terms which could have led to the omission of relevant publications.

Conclusion:

In the past few years, there has been an increase in human research on the intestinal microbiota-brain axis and psychological wellness. Overall, the reviewed literature supports the importance of gut microbiota-brain interactions in human mental illnesses, including the impact of probiotics on mental health outcomes and brain connections.

Conflict of Interest: There were no conflicts of interest.

Funding: No funding was received for the study.

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