Probiotics and the microbiota-gut-brain axis: focus on patients with depression. A review of current research

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This review covers recent data on the relationship between major depressive disorder (MDD) and faecal microbiome and examines the co-relations between the use of probiotics and changes in psychiatric state.
We conducted a thorough search of academic databases for articles published between 2018 and 2022, using specific keywords and previously established inclusion/exclusion criteria regarding faecal microbiota, depressive disorder, and probiotics. Of 192 eligible articles (reviews, original papers, and clinical trials), we selected 10 that fully met our criteria and performed a careful review to determine any correlation between microbiome, probiotic treatment, and depression. All patients were adults (mean age, 36.8), with at least one MDD episode and onset of depression during adolescence (duration of 31.39 years of depressive episodes). We found mixed but mostly positive results regarding the influence of probiotic/prebiotic/postbiotic effects on depression. We could not identify the precise mechanism of action that led to their improvement. Antidepressants did not alter the microbiota, according to studies that evaluated this aspect. Probiotic/prebiotic/postbiotic treatments were proven to be safe, with few and mild side effects.
Probiotics seemingly could be beneficial in patients with depression, as evidenced by well-established depression scales. Based on this finding and the high tolerability and safety of probiotics, no caveats against their routine use can be made. Some unmet needs in this field include determination of the dominant type of microbiota in specific patients with depression; study of microbiome-directed/driven treatment regarding dose and duration adjustments; and multiple versus single strain treatments.

Key words: microbiota, depression, depressive disorder, probiotics

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INTRODUCTION

Major depressive disorder (MDD) is one of the most widespread mental illnesses with a high disability rate, affecting more than 350 million people worldwide[1]. The lifetime prevalence of MDD is approximately 5–17% percent, with a 2:1 female: male ratio possibly due to hormonal differences, the effects of childbirth, and different psychosocial stressors. MDD has a multifactorial aetiology including biological, genetic, environmental, and psychosocial causes. The diagnosis of MDD is based on the Diagnostic and Statistical Manual of Mental Disorders. Regarding these criteria, depressive symptoms must be present most of the day, nearly every day and at least one of the symptoms must be either depressed mood or loss of interest/pleasure, causing social or occupational impairment[2]. In addition, the emergence of the coronavirus disease 2019 pandemic has been associated with an increase in the prevalence of mental illnesses such as MDD (ref.[3]).

The human gut is a complex microenvironment including more than 100 trillion microorganisms known as gut microbiota, mainly composed of bacteria, viruses, fungi, and archaea, which communicate bi-directionally with the host's central nervous system. Earlier studies revealed the importance of this biochemical signalling pathway, referred to as the "microbiota-gut-brain axis". These studies also postulated that this axis might influence cognition and mood via hormonal, metabolic, neural and immune-mediated mechanisms[4]. Perturbations in the composition of intestinal microbiota are referred to as dysbiosis and occur due to many conditions such as gastrointestinal tract disorders, cardiovascular diseases, diabetes, obesity, metabolic syndrome, human immunodeficiency virus infection, and psychiatric disorders. Conversely, gut dysbiosis is frequently observed in patients with psychiatric disorders, such as those with MDD. Recent studies have identified certain anomalies in the diversity of microflora in patients with depression, including a reduction in Firmicutes abundance compared with healthy controls: decline in growth of Faecalibacterium genera and overrepresentation of Bacteroides, Proteobacteria, and Actinobacteria in faecal samples[5-7].

Probiotics are live microorganisms that can produce health benefits in hosts, even in patients with MDD, when consumed in adequate amounts. They have the potential to restore and sustain microbial balance and intestinal homeostasis, most likely via the microbiota-gut-brain axis.

One study showed the potential of probiotics to alleviate the symptoms of depression and reduce the grade if

probiotics are ingested in adequate amounts, particularly in association with antidepressants, for at least 4 weeks[8].

We aimed to identify and analyse the most recent research regarding the relationship between MDD and the microbiome and determine any correlation between the use of probiotics, antidepressants, and changes in the psychiatric state of participants.

MATERIALS AND METHODS

Search method

We conducted a thorough search of the PubMed, Springer, Scopus, Web of Science, and Science Direct databases for all types of articles. The publishing date of the articles was restricted to the period between 2018 and 2022. The main keywords searched were: "microbiota-gut-brain axis", "depression", "depressive disorder" and "probiotics". The search was limited to English language and human studies on the effects of probiotics on patients with depressive disorders or depression-related symptoms. The search was conducted separately by all authors of this paper, after which matched papers were used.

Inclusion and exclusion criteria

Our first inclusion criterion was for the period of 2018–2022. The remaining inclusion criteria were as follows: open access studies including human participants or mixed (human and animals) and adult patients (aged over 18 years). These criteria included interventional studies that involved administering probiotics to patients with previously diagnosed depressive disorder based on specific evaluation scales (previously diagnosed by a psychiatrist with mild-to-severe MDD) and studies that performed microbiome analysis in their participants. Of note, all inclusion criteria were concomitantly met.

We excluded all articles (except for one that was conducted on both humans and mice) on experiments and studies conducted solely on rats, as they were not clinically relevant to the effects of probiotics on humans. Second, other exclusion criteria included the presence of multiple psychiatric disorders. Thus, we did not consider articles on studies in patients who experienced a combination of depression with anxiety or schizophrenia with depressive and catatonic episodes because the probiotic effects and benefits were not limited to just the depressive episodes. Although these studies showed the positive effects of probiotics in patients with complex psychiatric disorders, they did not specifically focus on depressive episodes, with the most complex psychiatric syndromes at hand (attention deficit hyperactivity disorder and schizophrenia).

We excluded research articles published earlier than 2018 because we searched for the most relevant articles that used updated methods and solutions for treating patients with depression with probiotics, as well as the fact that the reviews from 2018 analysed data from previous years. Notably, some of the methods used in the studies between 2018 and 2022 had not discovered previously (the fingerprinting method that associated different fingerprinting microbiota with certain depression phenotypes). In addition, we paid attention to the fact that the reviews we used did not comprise the analysis of the rest of the trials/research articles we analysed not to duplicate the information.

Synthesis and extraction of data

Our team reviewed the selected articles for inclusion and data extraction (Fig. 1). After the selection of articles, we extracted the following parameters and data: study design and number of included patients and matching controls, duration of the study (follow-up), and treatment period. These data also comprised characteristics of the studied population (sex, age, and clinical diagnosis). Data on conclusions regarding the characteristics of the microbiome in participants with depression versus controls and conclusions regarding the effects of probiotic administration on depression and on microbiome; and types of probiotics used and method of use were also extracted. For methodological purposes, accuracy of data, and relevance of results, we separately analysed the reviews from the personal research/trial papers.

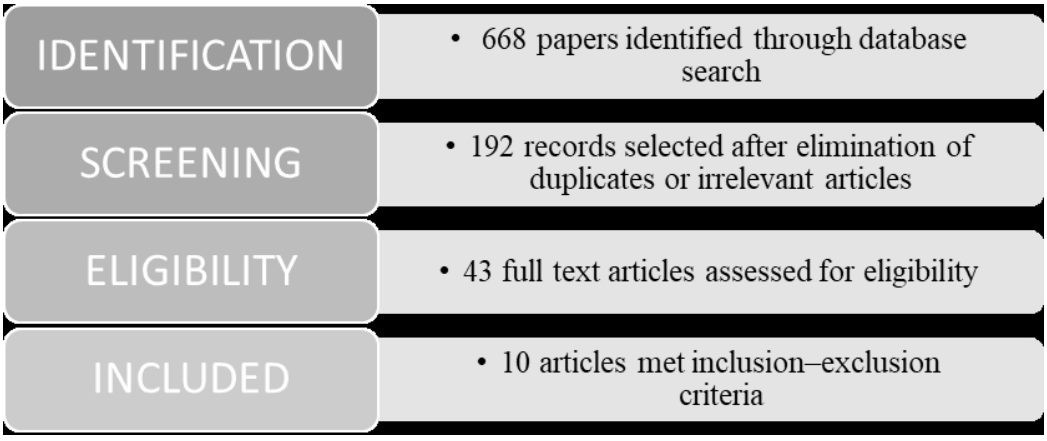

Fig. 1. Selection of the studies for the review.

Table 1. The analysis of research studies/trials.

Study	Type	Patients	Male/ female	Mean age	Probiotics	Dose/ administration	Microbiome testing	Depression test	Outcome
Chahwan et al., 2019	Triple blind RPCT	91 (71 depr+ 20 non depr)	27/64	36.06	Probiotic powder mixture (Ecologic Barrier)	2x2g/sachet ($2.5x10^9$ CFU/g)	16s rRNA gene sequencing	MINI DASS-21 BDI-II BAI LEIDS-R	Possible effects on cognitive patterns associated with depression
Reininghaus et al., 2020	RPCT	82 (40+42 placebo)	18/64	Not provided	Probiotic mixture OMNi-BiOTiC® Stress Repair	3g/day ($7.5x10^9$CFU/3g)	16s rRNA gene sequencing	MINI	Positive influence on somatic comorbidities without alleviating depression symptoms
Chen et al., 2021	Non randomized, open label	11 (MDD)	3/8	39.4	PS128 (BENED Biomedical Co. Ltd.) Lactobacillus plantarum	2x1cps (2x300mg)/day ($3x10^{10}$ CFU/cps)	16s rRNA gene sequencing	HAMD-17 DSSS	depressive severity significantly ameliorated
Tian et al., 2022	Double blindRPCT	45 (25 placebo, 20 medication)	15/30	49.7	*Bifidobacterium breve* CCFM1025 (Shisheng Yisheng (Yangzhou), Co., Ltd)	1sachet/day (10^{10} CFU)	16s rRNA gene sequencing	HDRS-24 MADRS BPRS	Positive effect on atenuation of depression

RPCT, randomised placebo-controlled trial; CFU, colony forming unit; rRNA, ribosomal ribonucleic acid; MINI, Mini International Neuropsychiatric Interview; DASS, Depression Anxiety Stress Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; LEIDS-R, Leiden Index of Depression Sensitivity-Revised; HAMD/HDRS, Hamilton Depression Rating Scale; DASS, Depression Anxiety Stress Scale; MADRS, Montgomery-Asberg Depression Rating Scale; BPRS, Brief Psychiatric Rating Scale.

Table 2. The analysis of reviews.

Study	Type	Papers/patients	Probiotics	Microbiome testing	Depression test	Outcome
Ng et al., 2018	Meta-analysis (human studies)	10/1349	probiotics	yes	yes	Overall insignificant effect on mood
Goh et al., 2019	Meta-analysis (human studies)	19/1901	probiotics	no	yes	Significantly beneficial effect on MDD
Liu et al., 2019	Meta-analysis of clinical trials (human)	34/not provided	pre and probiotics	no	yes	No ameliorative effect on MDD and anxiety
Nadeem et al., 2019	Review of reviews	7/not provided	probiotics	partially	yes	Definitive effect cannot be concluded
Chudzik et al., 2021	Review (preclinical and clinical trials)	22/663	probiotics, prebiotics and postbiotics	yes	yes	Beneficial role on the brain-gut-microbiota axis in animal models with depression
Loniewski et al., 2021	Review	28/2167	probiotics	yes	yes	Possible effects on MDD

MDD, major depressive disorder.

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RESULTS AND DISCUSSION

Essential study characteristics

Using the above-mentioned keywords in the initial search, we found a total number of 668 articles: 468 articles at Science Direct, 77 articles at Web of Science, 51 articles at Springer, 45 articles at PubMed, and 27 articles at Scopus.

Of the 668 initially included articles, 476 were excluded as duplicate or irrelevant articles. The remaining 192 were eligible full-text articles. Of these, only ten met the inclusion criteria. We later checked all the reference lists of the selected 10 articles for relevant articles that might have not been shown during our initial search. However, we did not identify any new articles that met our criteria. The key details of each study were extracted and are summarised in Tables 1 and 2.

Thus, in the end, our selection comprised 10 papers. Although these papers shared similar purposes, they significantly differed in terms of design and methods. We selected six reviews of the published literature, namely the papers by Loniewski et al. (published in 2021) (ref.[9]) and Goh et al. (published in 2019) (ref.[10]) focusing on both observational and interventional previously existing studies (16+19 studies in total), and the meta-analysis by Ng et al. in 2018 (ref.[11]) who included 10 clinical trials with more than 1000 participants. Another very interesting review was the work by Chudzik et al. in 2021 (ref.[1]), who analysed not only clinical data but also preclinical information from animal and human models, concluding that for the animal model, there was a significant influence of probiotics on depression that needs further trials in humans. The review by Liu et al. focused on depression and anxiety and found a modest influence of probiotics in individuals with depression, which was of interest to us, as we did not focus on anxiety. The well-documented work by Nadeem et al. in 2019 (ref.[12]), was a review of reviews focusing on previous randomised trials, with mixed conclusions. One study (Chahwan et al. published in 2019) (ref.[13]) was the publication of a triple-blinded, randomised, placebo-controlled clinical trial that analysed the microbiome before and after medical intervention with a specific probiotic product in patients with mild-to-severe depression. Similar to this study, the open trial by Chen et al. in 2021 (ref.[14]), which positively demonstrated the influence of probiotics on depression, using a specific strain of probiotics in a small cohort of patients with depression. The well-designed paper of Reininghaus et al. in 2020 (ref.[2]), analysed the direct effects of probiotics alone or in combination with biotin in patients with depression and showed beneficial results. The last study we included (by Tian et al.) (ref.[15]) was a very recent trial in 2022, which was a RPCT using a single strain of probiotics and demonstrated beneficial effects on depression.

All patients that were considered from the 10 articles that met our criteria were previously diagnosed with MDD by a psychiatrist (mild-to-severe forms). To diagnose MDD, 10 studies used several depression-measuring scales, such as the Epworth Sleepiness Scale, Fatigue Severity Scale, Hamilton Anxiety Scale, and Hamilton Depression Scale.

Clinical characteristics of the included subjects

Therefore, if we add up the number of patients studied in these papers, we have a significant number of 6309 participants, with the mention that two reviews comprising 41 trials did not provide the number of patients. However, it might be suggested that these reviews included thousands of participants, allowing us to assume that correct conclusions could be drawn from such extensive cohorts of people.

All patients were adults aged 18–55 years at the time of the study, with an average age of 36.8. The evaluated patients had an onset of depression during their teenage years, with an average commencing age of 14.06 years and with the duration of 31.39 years of their depression and depressive episodes. The patients were both women and men with relatively consistent dietary habits, similar weights with an average of 24.47 kg/m2 and similar education statuses, spending an average of 14.08 years of schooling. All the patients had at least one major depressive episode.

Microbiome data and analysis

In addition to the psychiatric scales mentioned, the studies also used 16s rRNA sequencing techniques to properly characterise the gut microbiota in stool samples provided by the patients.

All patients with MDD in the selected studies had disturbances of different types in the gut microbiome. Patients with MDD who participated in interventional probiotic trials were either in the placebo group or probiotic group.

The studies included different sample characteristics, with variable follow-up and treatment durations, as well as variable therapeutic strains, and safety and outcome assessments.

All clinical trials included in our study focused on the administration of different types and strains of probiotics, such as *Lactobacillus plantarum*, *Bifidobacterium breve* or probiotic mixtures. At the same time, most of the reviews included in our study also included probiotic research. Therefore, we could conclude that probiotics are the most studied compounds in this particular pathological context. In addition, we could also conclude that the dosage administered in patients with MDD was the same as that in the placebo group/healthy controls, and basically it was the manufacturer's standard recommended dose for dysbiosis without any adaptation and in general for a duration between 4 and 8 weeks.

We found both negative and positive findings regarding the influence of probiotic/prebiotic/post-biotic effects on depression. The most recent trial by Tian et al. in 2022 showed positive effects on attenuation of depression, and at the same time the most recent review by Loniewski et al. in 2021 showed possible effects on MDD.

Studies that compared the microbiota before and after treatment (in general at baseline, at week 4, or week 8) between the control and depressed groups found no sig-

nificant differences. Therefore, basically no phyla differed significantly between baseline and after the therapeutic (probiotic) intervention: there were also no differences between alpha and beta diversity. Thus, the dosage of the probiotic was probably not sufficient to be detected in the faeces. However, this dosage might still have had an effect on the psychological sphere. Therefore, based on our review, we did not have a clear indication of the mechanism of action, which could probably be explained by engagement in the daily preparation of the therapeutic product and adherence to the program meant to improve well-being. Notably, antidepressants did not alter the microbiota according to studies that considered this aspect.

Probiotic/prebiotic/postbiotic treatments were proven to be safe and well tolerated, with few and mild or no side effects. Therefore, no recommendation against their routine use in patients with depression can be made.

DISCUSSION

Initially, the association between depression and intestinal microbes was unexpected. However, it is now well-known that depression is associated with several changes in the gut microbiota[5]. In the last couple of years, research has revealed a bidirectional communication system between the gut microbiota and the central nervous system, known as the gut-brain-axis, which is fulfilled through multiple pathways, particularly involving neural, immunological, metabolic, and hormonal-mediated mechanisms[2,14].

Several studies have shown evidence of different microbiota compositions in patients with MDD compared with healthy individuals, and these patients have diminished gut microbial diversity[5]. In addition, this major finding was met in all studies analysed in our review. Therefore, a great consensus can be clearly affirmed regarding this association.

However, our review did not reveal whether this interconnection between microbiota dysregulation and MDD was bi-directional or which of the two entities provoked the other. At the same time, although several studies have described a bidirectional interconnection between MDD and the gut microbiota, it is undecided whether depression was the cause or effect of gut microbe's dysregulation[6].

A randomised, triple-blind, placebo-controlled trial of probiotics for depressive symptoms study[4] including 71 participants demonstrated improvement in symptoms in all participants. This suggests that there was a benefit of the non-specific therapeutic effects associated with the weekly monitoring visits performed by the physicians in charge of the study. The 71 participants were randomly assigned to two groups and allocated to either the probiotic or placebo daily over the course of 8 weeks. The probiotic group showed a significantly greater reduction in cognitive reactivity, particularly in patients with mild/moderate depressive episodes. However, probiotics did not significantly alter the microbiota in patients with depression. The research papers we reviewed also suggested that even in the placebo groups, there was still an improvement in the depression scales: not always supported by changes in the microbiota composition. These studies indicated that this positive effect was based on occupational patterns and engagement in trial activity.

Most of the papers we reviewed used the same advanced technique for microbiota determination (rRNA gene sequencing). Although the previous review papers we compared with ours used more basic techniques, the results were usually similar in terms of the most disturbed bacterial strains (mostly Lactobacillus and Bifidobacterium species) (ref.[14,15]). Therefore, most interventional studies relied on administration of these particular strains. Of note, all the studies from our review and the older ones adhered to standard dose administration and standard duration of administration, with no particularisation based on microbiome testing, which we suggest that it should be more beneficial.

Another aspect that is in general agreement not only in our review but also in previous papers is that probiotic/prebiotic/postbiotics could not be recommended instead of the standard treatment for depression, but they are safe for co-administration.

CONCLUSION

After analysing the most recent and relevant medical data on depression, microbiota, and the influence of probiotic treatment, we can conclude that there appears to be a beneficial role of probiotics in patients with depression, evidenced by well-established depression scales. However, there is no clear indication of the mechanism of action or quantification of their positive effects. Owing to this positive effect and their high tolerability and safety, no recommendation against their routine use in patients with depression can be made. Further larger studies must be conducted, particularly with attention to other aspects such as gut permeability and integrity markers, dose and strain adaptation of treatment driven by microbiome findings, and extended follow-up duration. We can also conclude that there are still some unmet needs in this field that should be considered for further research, such as the determination of the exact dominant type of microbiota in patients with depression, the study of microbiome-directed/driven treatment with dose and duration adjustments, and multiple versus single strain treatments. We suggest that future research would shed more light into this important pathological issue.

Search strategy and selection criteria

Our search strategy comprised previous published papers related to the microbiota of the patients with depressive disorders and the influence of probiotic treatment upon these patients. We searched for original articles published in English language, between 2018 to 2022 in the following renowned databases: PubMed, Springer, Scopus, Web of Science and Science Direct. The search terms in our paper were: "microbiota-gut-brain axis", "depression", "depressive disorder" and "probiotics".

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