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GUT MICROBIOTA, MOOD AND DISORDERS OF GUT-BRAIN AXIS

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Abstract – The main objective of this review is to summarize recent studies on the role of microbiota and microbial-targeted therapeutics in symptom relief and mood regulation of IBS patients.
A PubMed search was performed to identify publications on the role of microbiota in disorders of the gut-brain axis published between March 2023 and March 2024.
Six studies were included in the review: four on the effects of probiotic supplementation on GI IBS symptoms, mood, and microbiota, and two on the effects of specific diets on GI IBS symptoms, mood, and microbiota. In the first group of studies, probiotics containing the *Bifidobacterium* genus were applied. All studies reported a significant reduction of overall IBS symptoms, and most studies additionally reported a significant decrease in anxiety and/or depression in the intervention group compared to the placebo group. Some changes in bacterial abundance were reported. In the second group of studies, the Mediterranean diet and the low FODMAP diet both had a significant impact on GI symptom reduction, while the Mediterranean diet also improved depressive symptoms. Only the low FODMAP diet had a significant effect on microbiota composition.
Probiotics and dietary interventions (Mediterranean and low FODMAP diet) could be useful for IBS symptom management. Additionally, these interventions may be beneficial for improving depression and anxiety symptoms in IBS patients.

Keywords: IBS, Microbiota, Mood, Depression, Anxiety, Symptom severity, Probiotics, Low FODMAP.

INTRODUCTION

Irritable bowel syndrome (IBS) is the most prevalent disorder of gut-brain interaction (DGBI), characterized by abdominal pain associated with altered bowel habits. The majority of patients also report associated anxiety and depression[1,2].

Based on the fact that a large number of individuals who meet the diagnostic criteria for an anxiety and/or depressive disorder have IBS and *vice versa*[2,3], we can postulate a possible direct connection between altered mood and microbiota in IBS patients. Also, we can presume that microbial-targeted therapeutics in depression and anxiety may have benefits for IBS patients as well.

The existence of a complex bidirectional communication system between the gut and the brain (gut microbiota-brain axis) improves our understanding of the close link between gut microbiota composition and various mood disorders[4,5]. It is apparent that major depressive disorder is associated with microbial dysbiosis related to alterations in microbial diversity[6-8]. On the one hand, depression can alter the composition of the gut microbiota and even lead to a gastrointestinal

disorder, such as IBS, and *vice versa*; disturbances in gut microbiota can worsen anxiety and depression[9]. Gut dysbiosis triggers systemic inflammation related to the increased release of proinflammatory cytokines, which affect brain function, possibly causing depressive symptoms[8]. For example, Kelly et al[10] showed that incidences of *E. coli* subtypes led to increases in depression and anxiety-related symptoms among the affected population. We must keep in mind that it is not yet clear whether alterations in the microbiota trigger pathological changes or coexist with them[11].

Despite that, a balanced composition of the gut microbiota and their metabolites has significance for general host health. Therefore, targeting the microbiota in the treatment of IBS and accompanied mood disorders may be a promising approach[12]. It has been demonstrated that it is beneficial to combine the administration of antidepressants with probiotics that contain specific types of bacteria[13].

This review summarizes recent advances in examining the role of the microbiota and microbial-targeted therapeutics in symptom relief and mood regulation (mainly anxiety and depression) of IBS patients.

MATERIALS AND METHODS

We performed a PubMed search for publications on gut microbiota and mood in IBS patients, published between March 2023 and March 2024. We applied the following filters: custom date range (March 2023 – March 2024) and article type (clinical trial, meta-analysis, randomized clinical trial). The following search query was used: (((((microbiota) AND (depression)) OR (mood))) AND (irritable bowel syndrome)) OR (gut brain disorders). Only articles published in English were included in the review. We selected only studies with adult participants (age 18 and above) with IBS or other disorders of the gut-brain axis, with a focus on gut microbiota and a report on the participants' mood (or, more specifically, depression). Two authors (MT & SPT) independently assessed study eligibility.

RESULTS

The search yielded a total of 57 articles. The articles were screened based on the inclusion and exclusion criteria. Forty-eight studies were excluded at the title and abstract stage (35 did not involve patients with disorders of the gut-brain axis, 10 did not focus on the microbiota, 2 did not involve adult participants, and 1 was a study protocol), which left 9 studies for screening at the full-text stage (Figure 1).

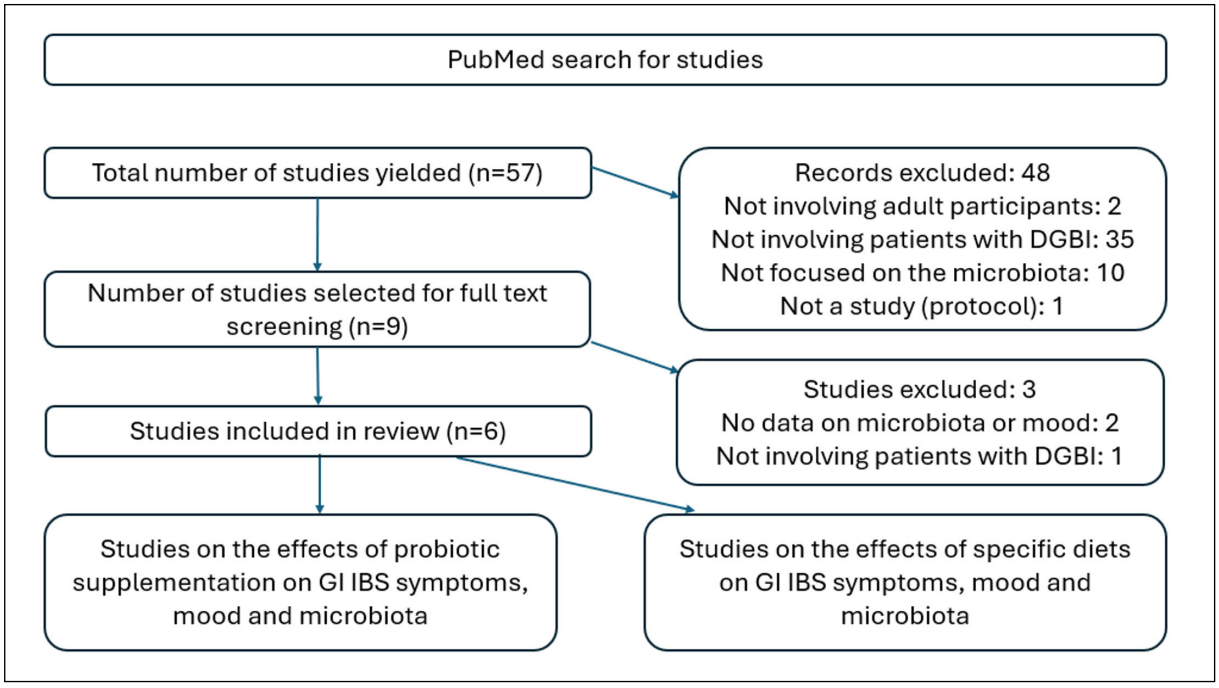

Figure 1. Flowchart of study identification, exclusion and inclusion.

Three additional studies were excluded at the full-text stage: one was a meta-analysis of studies on fecal microbiota transplantation in IBS patients, but no data was provided on microbiota or mood as outcome measures; one was a study on educational methods for the low fermentable oligo-, di-, monosaccharides and polyols (FODMAP) diet which also did not present data on microbiota or mood, and a third study did not include patients with disorders of the gut-brain axis. This resulted in six studies that were included in the review (Table 1). Four of these studies[14-17] examined the effects of probiotic supplementation on gastrointestinal (GI) IBS symptoms, mood, and microbiota, while the remaining two[18,19] explored the effects of a Mediterranean diet or a low FODMAP diet on GI IBS symptoms, mood, and microbiota.

Effects of Probiotic Supplementation on GI IBS Symptoms, Mood, and Microbiota

Out of the four studies[14-17] investigating the effects of probiotic supplementation on GI IBS symptoms, one[16] did not involve a measure of symptom severity, and another[17] had no direct microbiota measures but also involved the administration of probiotics. Thus, some data was only available in three out of the four selected studies.

All four studies[14-17] were randomized, double-blind, and placebo-controlled studies. All of them were conducted with IBS patients, mostly diarrhoea-predominant (3 studies)[14, 16, 17], and in one study[15], the participants were female IBS patients of all subtypes. The probiotic supplementation period (duration of intervention) lasted from 4 weeks[14] to 12 weeks[17], with only one study[14] reporting data after a follow-up period. In all four studies, the probiotics included the *Bifidobacterium* genus: in 2 studies[16, 17] *Bifidobacterium longum* was administered, one study[14] used a combination of *Bifidobacterium infantis, Lactobacillus acidophilus, Enterococcus faecalis* and *Bacillus cereus)*, while the fourth study[15] used a combination of *Lactobacillus acidophilus*, *Bifidobacterium bifidum* and *Bifidobacterium animalis*.

A significant reduction of overall IBS symptoms was reported by all three studies[14, 15, 17], particularly a reduction in pain (3 studies) and diarrhoea (2 studies)[14, 15]. In two out of four studies[15, 17], there was a significant decrease in anxiety and depression in the intervention group compared to the placebo group, while one study[14] reported no changes in mood, and one[16] did not report changes in mood between or within groups, but rather relationships between mood and metabolites, amygdala activation and microbiota abundance. Interestingly, the latter study[16] reported significant correlations between anxiety and depression reduction and the increased abundance of *Bifidobacterium longum,* as well as higher plasma concentrations of N-acetyl-tryptophan and butyric acid in the intervention group compared to the placebo group. This suggests that a possible mechanism for the central effects of *Bifidobacterium longum* could be tryptophan metabolism. Alpha diversity of microbiota was reported only in 2 studies[14,15], and no significant changes or differences between groups were observed. The same two studies[14,15] examined and reported significantly increased abundance of several bacterial taxa after probiotic administration compared to placebo.

To summarize, the authors of all four studies[14-17] conclude that the use of probiotics in IBS symptom management is promising and seems to be effective for short-term alleviation of GI symptoms and possibly depression and anxiety in IBS patients.

Effects of Specific Diets on GI IBS Symptoms, Mood, and Microbiota

Clinical guidelines for IBS and related DGBI stress the importance of including dietary treatments as a fundamental component of patients' care. Two final studies[18,19] focused on the effects of specific diets, Mediterranean (MD) and FODMAP diet, on GI symptoms, mood, and microbiota in IBS patients and coeliac disease patients with IBS-like symptoms.

Staudacher et al[18] investigated the effects of a Mediterranean diet (rich in vegetables, fruit, bread, cereals, legumes, nuts, and olive oil) on GI IBS symptoms, mood, and microbiota. This randomized controlled trial with 48 participants showed that MD is feasible in IBS and leads to improvement in GI and psychological symptoms. More precisely, 83% of the MD group reported improvement in global GI symptoms compared with 37% of controls, and 62% reported improvement in depressive symptoms compared with 23% of controls. However, there were no notable changes in microbiome composition in this study. Based on these findings, the authors conclude that MD is a healthy diet pattern associated with a reduced risk of disease which targets the gut-brain axis rather than just the gut.

TABLE 1. RECENT STUDIES ON MICROBIOTA AND MOOD IN DGBI.

Topic	Study design	Participants	Duration of intervention	Main findings	Study
Effects of probiotic supplementation on GI IBS symptoms, *mood* and **microbiota**	Randomized, double-blind, placebo-controlled, multicentre trial	IBS-D patients; probiotic group (probiotic tablet containing *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Enterococcus faecalis* and *Bacillus cereus*) n=122, placebo group n=121	2-week screening period, 4-week treatment period, and a 2-week follow-up period	– Overall symptoms, and particularly pain and diarrhoea were significantly reduced in the probiotic group, which was maintained through follow-up – Urgency of defecation, quality of life, anxiety and depression were not significantly improved in the probiotic group compared to placebo – No significant changes in alpha diversity were observed in either group; there were no differences in alpha diversity between groups – No change in beta diversity between groups after probiotic implementation – Compared to placebo, probiotics administration significantly increased the abundance of *Butyricimonas*, *Pseudobutyrivibrio*, *Barnesiella*, and *Sutterella* at the genus level – Probiotics increased the concentration of short-chain fatty acids and inhibited the decrease of propionic acid, compared with placebo	Bai et al[14]
Effects of probiotic supplementation on GI IBS symptoms, *mood* and **microbiota**	Double-blind, randomized, placebo-controlled superiority study	Female IBS patients; active group (probiotic capsule containing *Lactobacillus acidophilus, Bifidobacterium bifidum* and *Bifidobacterium* animalis) n=27, placebo group n=29	8 weeks	– Significantly lower symptom severity score in active group compared to placebo group (for individual symptoms: lower abdominal pain severity, bloating severity, number of days with abdominal pain, dissatisfaction with bowel habit and IBS impact on everyday life; lower proportion of loose stools and higher proportion of normal stools in the active group) – Significant decrease in symptom severity score after 8 weeks only in active group – Significant decrease from baseline in anxiety, depression, and avoidance and control behaviour only in the active group – No group differences in alpha diversity – Differential abundance analysis showed several bacterial taxa that were different between groups at endpoint but not at baseline (*Roseburia, Holdemanella, Blautia* and *Agathobacter* were more abundant in the active group, while *Ruminococcus*, *Roseburia, Prevotella, Blautia, Bacteroides*, and *Anaerostipes* were more abundant in the placebo group	Mullish et al[15]
Effects of probiotic supplementation on IBS *mood*, **microbiota**, blood metabolites and amygdala activation	Randomized, double-blind, placebo-controlled, single-centre pilot study	IBS patients with diarrhoea or alternating bowel habits; probiotic group (powder containing *Bifidobacterium longum*) n=18, placebo n=20	6 weeks	– A minimum two-point reduction in either depression or anxiety was associated with an increased abundance of *Bifidobacterium longum* – Probiotic group exhibited higher plasma concentrations of N-acetyl-tryptophan and butyric acid, compared to placebo group – Butyric acid levels correlated negatively with depression scores and amygdala activation – Decrease in amygdala activation was associated with higher levels of tryptophan, N-acetyl tryptophan and pentadecanoic acid – Plasma level of butyric acid was positively correlated with the abundance of *Bifidobacterium longum*	Martin et al[16]

Continued

TABLE 1 *(CONTINUED)*. RECENT STUDIES ON MICROBIOTA AND MOOD IN DGBI.

Topic	Study design	Participants	Duration of intervention	Main findings	Study
Effects of probiotic and postbiotic supplementation on GI IBS symptoms and mood	Randomized, double-blind, placebo-controlled, parallel-group, multicentre, three n arms study	IBS-D patients; probiotic group (capsules containing Bifidobacterium longum) n=63, postbiotic group (heat-treated Bifidobacterium longum) n=66, placebo group n=65	12 weeks	– a significant decrease in symptom severity in the two intervention groups compared to placebo – a significant reduction in abdominal pain severity, anxiety and depression in the two intervention groups compared to placebo group – a significant improvement in IBS-QoL scores in the two intervention groups compared to placebo group	Srivastava et al[17]
Effects of a Mediterranean diet on GI IBS symptoms, *mood* and **microbiota**	Randomized controlled trial	IBS patients, intervention group (Mediterranean diet) n=24, control group n=24	6 weeks	– a significant decrease in global symptom scores, as well as abdominal pain and bloating in the intervention group compared to control – lower anxiety and depression in the intervention group compared to control group – a greater reduction in anxiety and depression in the intervention group compared to control group, and a greater proportion of participants achieving a minimal clinically important difference in the intervention group compared to control group – IBS-QoL scores were higher in the intervention group compared to control group – no differences in alpha diversity, beta diversity, or species abundance between intervention group and control group; no changes between baseline and Week 6 in either group	Staudacher et al[18]
Effects of low FODMAP diet on GI IBS symptoms and microbiota	Clinical study	Coeliac disease patients with persistent IBS-like symptoms; low FODMAP diet (LFD) group n=34, control group n=36	4 weeks	– beta diversity of faecal microbiota was greater for the LFD group – no differences in alpha diversity after intervention period – less change in overall microbiota structure was weakly associated with larger reduction in diarrhoea in the LFD group – less change in overall microbiota structure was weakly associated with larger reduction in constipation in the control group – lower concentrations of short-chain fatty acid propionic and valeric acid in participants with initially high concentrations in the low FODMAP group	Herfindal et al[19]

IBS-QoL = irritable bowel syndrome quality of life; FODMAP = fermentable oligo-, di-, monosaccharides and polyols.

Herfindal et al[19] studied the effects of a low FODMAP diet on GI IBS symptoms and microbiota in individuals with treated coeliac disease (CeD). The main focus of this study was a detailed investigation of microbiota composition and its relationship with symptom severity; however, no measures of mood were included. In this randomized control trial, 39 participants consumed a combined low FODMAP diet and gluten-free diet (GFD) for 4 weeks, while 36 participants continued with GFD. A low FODMAP diet had a significant impact on the composition of fecal microbiota and related variables of gut health in GFD-treated CeD patients with persistent GI symptoms. The low FODMAP diet resulted in lower concentrations of short-chain fatty acids (propionic and valeric acid) in participants with initially high concentrations. However, the measured biomarker of gut inflammation was unaffected by the diet. Also, few uniform abundance changes of specific bacterial taxa within the low FODMAP diet group were observed, indicating a highly individualized microbial response to the diet.

It is interesting to note that the Mediterranean diet and the low FODMAP diet are completely contrary to each other (high *vs.* low FODMAP), but according to these findings, they both seem to have beneficial effects on IBS symptoms.

DISCUSSION

During the past year significant progress has been made regarding the investigation of probiotic and diet effects on GI symptoms and microbiota composition in IBS patients. The studies included in this review offer promising results for clinicians and patients regarding the safety and efficacy of these approaches in symptom management.

However, although the studies point to similar conclusions, they also illustrate the need for a more structured and uniform approach in the future. The field of microbiota research is vast and offers numerous measures and bacterial taxa that can be considered. Also, there are multiple approaches to measuring psychological states, traits, and, in the context of IBS, symptom alleviation. Perhaps most importantly, except for research by Bai et al[14], all studies reviewed here had relatively small sample sizes.

All of this has resulted in a diversity of findings which does not allow for drawing definitive conclusions. Thus, the focus of future research should be carrying out more randomized, double-blind, placebo-controlled studies with larger sample sizes. Hopefully, replication studies will revisit findings on the benefit of specific probiotic strains and/or combinations, providing more evidence in favour or against their application. This may lead to incorporating probiotic use into guidelines for symptom management, if they truly prove to be effective, as the studies reviewed here suggest.

CONCLUSIONS

Findings suggest that probiotics and dietary interventions (particularly Mediterranean and low FODMAP diets) could be useful for IBS symptom management. Additionally, these interventions may improve the effectiveness of standard antidepressant therapy in IBS patients with symptoms of depression and anxiety.

Conflict of Interest

The authors declare no conflict of interest.

Informed Consent and Ethics Approval

Not applicable due to the type of study.

Authors' Contributions

MT and SPT wrote the manuscript. GH critically reviewed the manuscript. All authors approved the final version of the manuscript.

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AI Statement

No AI tools were used for the production of the current manuscript.

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