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CAN WE FINE-TUNE MICROBIOME WITH PROBIOTICS?

M. Fiorani, S. Porcari, S. Bibbò, G. Cammarota, G. Ianiro

Department of Translational Medicine and Surgery, Università Cattolica del Sacro Cuore, Rome, Italy; UOC Gastroenterologia and UOC CEMAD Medicina Interna e Gastroenterologia, Department of Medical and Surgical Sciences, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

Corresponding Author: Marcello Fiorani, MD; e-mail: marcellofiorani94@gmail.com

Abstract – The therapeutic modulation of gut microbiota is a rapidly growing field of research, recognized as pivotal in the development of personalized medicine. In this context, probiotics have emerged as one of the main therapeutic tools, with increasing evidence supporting their efficacy in different clinical areas. In this review, we summarize the most relevant updates published during the past year regarding the use of probiotics in the management of various gastrointestinal and extraintestinal disorders.

Keywords: Probiotics, Gut microbiota, Irritable bowel syndrome.

INTRODUCTION

Gut microbiota is a dynamic collection of microorganisms, composed of trillions of microbes, both prokaryotes (bacteria and archaea), and eukaryotes (fungi, protozoa, and helminths), in addition to viruses[1], that coevolved alongside the human hosts[2]. Its taxonomic composition is highly variable between individuals due to multiple factors, such as dietary habits, lifestyle, genetics, environmental factors, and the microbiome's intrinsic interaction structure[3]. Numerous studies have confirmed that gut microbiota is involved in maintaining physiological homeostasis, influencing several key functions such as nutrient absorption, immune system regulation, and protection against pathogens[4,5]. On the other hand, the alteration of the composition and function of gut microbiota, with the disruption of homeostasis, has been associated with several disorders, including gastrointestinal[6], metabolic[7], neurological disorders[8], and cancer[9].

Hence, therapeutic approaches that modulate gut microbiota can potentially be applied to a wide range of clinical conditions, allowing the development of personalized therapeutic or prophylactic treatments. Moreover, other relevant fields of application are the prevention of chronic diseases[10], the improvement of the nutritional status of the host[11], and the modulation of the host's response to medical therapies[12,13].

Even though our knowledge of the human microbiota continues to grow, its clinical application is still in an early stage. The therapeutic strategies that are currently available have different aims and mechanisms of action, and while certain approaches, such as nutritional interventions or fecal microbiota transplantation (FMT), have a broad impact on the entire microbial community, others, such as probiotics, prebiotics, postbiotics, and phage therapy, can act more precisely on specific taxa or strains[12].

Beneficial taxa can be supplemented through the use of probiotics, which are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the

host[14], and they have been extensively studied in recent years, in the context of numerous clinical disorders[15]. The main available probiotics are bacteria, such as Bifidobacteria, Lactobacilli, Streptococci, and particular strains of *E. coli*, or yeasts such as *Saccharomyces boulardii*[16,17]. Probiotics can exert their effect through different mechanisms, including the production of substrates, like short-chain fatty acids (SCFA), the improvement of intestinal barrier function, and the inhibition of the growth of opportunistic pathogens[18].

However, the definition of probiotics includes many products with different and often scarcely specified characteristics, allowing questionable generalizations. Consequently, the evidence for probiotic use is still insufficient in numerous conditions where they could be potentially employed[19].

In 2012, in order to address these issues, the FDA defined the new category of live biotherapeutic products (LBP)[20]. LBPs are products containing live microorganisms, applicable to the prevention, treatment, or cure of a disease or condition in human beings[20,21]. Notably, LBPs are more precisely regulated, supporting the identification of specific indications for each probiotic strain as evidenced by clinical studies, which is essential for the progress of personalized medicine[22].

The therapeutic modulation of the gut microbiota through probiotics is, therefore, a highly significant field of research, and this review summarizes the most important advancements in this area published over the past year.

PROBIOTICS IN GASTROINTESTINAL DISORDERS

Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction characterized by a high prevalence and often associated with psychological comorbidities[23]. A randomized, double-blinded, placebo-controlled study[24] included 70 female patients affected by IBS and observed that the administration of a multistrain probiotic containing *Lactobacillus acidophilus* CUL60, *Lactobacillus acidophilus* CUL21, *Bifidobacterium bifidum* CUL20 and *Bifidobacterium animalis* subsp. *lactis* CUL34 significantly reduced the IBS-symptom severity score (IBS-SSS), anxiety and depression scores, and the IBS-related control and avoidance behavior score. The fecal microbiota showed significant differences in the abundance of *Roseburia*, *Holdemanella*, *Blautia*, *Agathobacter*, *Ruminococcus*, *Prevotella*, *Bacteroides*, and *Anaerostipes*. Another multi-center randomized controlled trial (RCT), comprising 317 patients with IBS-D, investigated the efficacy of *Lactiplantibacillus plantarum* Lpla33 and showed that after 8 weeks, the IBS-SSS was significantly reduced[25].

Srivastava et al[26] observed that *Bifidobacterium longum* CECT 7347 reduced the IBS-SSS and improved the quality of life of IBS-D patients, compared to placebo. Interestingly, a postbiotic obtained from the same strain was similarly effective. Other studies investigated the factors potentially associated with response to probiotics, finding that IBS-D patients with high abdominal pain scores could be more likely to respond to probiotic therapies[27]. Specific taxa could also predict probiotic efficacy: in particular, *Collinsella aerofaciens* appeared to be overrepresented in responder IBS patients[28].

Chronic constipation (CC) is another common gastrointestinal disorder, and various evidence suggests that dysbiosis plays a significant role in its pathogenesis[29]. A randomized, double-blind, placebo-controlled study, including 163 patients, evaluated the effect of *Lactiplantibacillus plantarum* P9 on CC[30]. The probiotic treatment improved the frequency of spontaneous bowel movements and complete spontaneous bowel movements and reduced the level of worries and concerns. The administration of *Lactiplantibacillus plantarum* P9 was associated with favorable changes in the fecal metabolome and with the enrichment of beneficial taxa, such as *Lactiplantibacillus plantarum* and *Ruminococcus_B gnavus*. The incidence of chronic constipation increases with age, and it has been shown that elderly subjects have a reduced abundance of bifidobacteria[31]. A Japanese RCT[32] examined the efficacy of *Bifidobacterium longum* BB536 in 79 elderly patients affected by CC, observing an improvement in the number of bowel movements.

Parkinson's disease (PD) is often associated with constipation, and its prevalence increases with the progression of the disease, reducing the patient's quality of life[33]. Constipation could be associated with gut microbiota alterations, as it has been described that in PD patients

there is a decreased abundance of Lachnospiraceae and Prevotellaceae, while Verrucomicrobiaceae are increased[34,35]. *Lacticaseibacillus paracasei* strain Shirota has shown encouraging results in a previous pilot study, improving stool consistency and defecation habits in PD patients[36]. These results have been confirmed by a recent RCT by Yang et al[37] who evaluated the effect of the administration of this strain in PD patients, observing a favorable effect on constipation-related symptoms.

Functional dyspepsia (FD) is a highly prevalent chronic disorder of gut-brain interaction, whose numerous pathophysiological mechanisms appear to be also associated with dysbiosis[38]. An RCT by Zhang et al[39] observed that the treatment with *Bifidobacterium animalis* subsp. *lactis* BL-99 for 8 weeks significantly improved the clinical response in FD patients, but the effect disappeared after 8 weeks from the end of the therapy. Interestingly, the authors reported an increased abundance of SCFA-producing microbiota and augmented levels of fecal and serum SCFA.

Another important cause of dyspeptic symptoms is *Helicobacter pylori* (Hp) infection[40]. A study by Niu et al[41] investigated the effect of *Lacticaseibacillus rhamnosus* LRa05 on the Hp eradication rate and the mitigation of the gastrointestinal side effects related to the bismuth quadruple therapy. Probiotic supplementation was associated with a non-significant trend toward a better eradication rate and a significant reduction of gastrointestinal symptoms. An additional study showed that *Lactobacillus rhamnosus* GG improved the remission of dyspepsia in HP patients who underwent bismuth quadruple therapy without significant differences in eradication rates and therapy-associated side effects[42].

PROBIOTICS IN EXTRAINTESTINAL DISORDERS

The gut-liver axis has been implicated in the pathogenesis and the progression of numerous liver diseases, outlining the relevant role of the intestinal barrier and dysbiosis[43]. The most common cause of chronic liver disease worldwide is metabolic-associated fatty liver disease (MAFLD)[44], known to be associated with microbiota alterations, including an increase in Proteobacteria[45]. A clinical study by Lin et al[46] examined the effect of different combinations of probiotics (comprising *L. fermentum* TSF331, *L. reuteri* TSR332, and *L. plantarum* TSP05) in patients with elevated baseline levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and uric acid (UA). After 60 days, the authors observed that in all the treatment groups, the serum levels of AST, ALT, and UA levels were significantly reduced. Another trial[47] examined patients affected by histology-proven nonalcoholic steatohepatitis (NASH) and showed that the administration of *Lactobacillus acidophilus* ATCC SD5221 and *Bifidobacterium lactis* HN019 reduced the AST to platelet ratio index (APRI score). Alcohol-associated liver disease (ALD) is often diagnosed in heavy drinkers, but currently, there is a shortage of effective therapeutic options. In a pilot study, *Lactobacillus rhamnosus* GG showed encouraging results, reducing the markers of liver injury and alcohol intake[48]. Probiotic therapies could also be effective in cirrhotic patients referred for liver transplantation, as shown by Ramachandran et al[49]. A multistrain probiotic was associated with improvements in the nutritional status and with a significant reduction of the Child Turcotte Pugh score of these patients.

The incidence of metabolic disorders and obesity has increased substantially in the last decades due to many factors, including increased food consumption and a sedentary lifestyle[50]. Gut microbiota is known to contribute to the pathogenesis of various metabolic disorders, regulating different mechanisms such as glucose and lipid metabolism, energy absorption, and chronic inflammation[51,52]. *Lacticaseibacillus paracasei* has shown beneficial effects in several murine models of metabolic disorders[53], and an RCT by Yang et al[50] evaluated its effects on endothelial function and cardiometabolic health in patients affected by metabolic syndrome. Probiotic supplementation resulted in improved endothelial function, potentially due to the reduction of remnant cholesterol levels. Regarding diabetes, a multi-strain probiotic containing *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Saccharomyces boulardii*, and *Bifidobacterium lactis*, led to encouraging results in 91 diabetic patients who received the probiotic treatment or placebo for 6 months. Compared to controls, the patients who received the multistrain probiotic showed significantly lower levels of total cholesterol, fasting blood glucose, and HbA1c[54].

Metformin is a cornerstone drug in the treatment of diabetes and is widely prescribed. One of the most significant issues associated with its use is the occurrence of gastrointestinal side effects, affecting up to 20% of patients[55]. A randomized, double-blind, cross-over trial[56] assessed the effectiveness of a multi-strain probiotic containing *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W51, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, Levilactobacillus *brevis* W63, *Lacticaseibacillus casei* W56, *Ligilactobacillus salivarius* W24, *Lactococcus lactis* W19, and *Lactococcus lactis* W58 in 37 diabetic patients with gastrointestinal side effects due to metformin treatment. The authors observed that the probiotic supplementation was associated with a significant reduction of nausea, abdominal bloating, abdominal pain, and diarrhea, together with an improvement in self-assessed tolerability of metformin[56].

The bidirectional and continuous relationship between the gut and the central nervous system is known as the gut-brain axis, and the recognition of the role of gut microbiota in their communication led to the concept of the microbiota-gut-brain axis. Gut microbiota modulates the gut-brain axis in multiple ways, including through endocrine, immune, and neural pathways. Numerous microbes are known to synthesize neurotransmitters, such as GABA, noradrenaline, and dopamine. Moreover, gut microbiota can produce neuroactive metabolites that influence behavior and neural activity through mechanisms still being explored[57].

Major depressive disorder (MDD) is one of the main causes of disability around the world[58], but its treatment still poses significant challenges, as almost one-third of patients receiving pharmacotherapy or psychotherapy achieve only partial remission from MDD[59]. A pilot RCT evaluated 49 patients affected by MDD with incomplete response to antidepressant medication and showed that a multi-strain probiotic combined with the ongoing antidepressant medication led to greater improvements in depressive and anxiety symptoms compared with placebo[60].

The neural mechanisms underlying the clinical effects of probiotics in MDD are still unknown, and to investigate these effects, a study used a multimodal neuroimaging approach in 32 patients affected by MDD receiving a probiotic treatment or placebo. Probiotics appeared to prevent neuronal degeneration along the uncinate fasciculus and to change fronto-limbic resting-state functional connectivity, and these structural and functional changes were associated with improved depressive symptoms[61].

Psychobiotics are also investigated in the management of anxiety. Test anxiety among college students is a very common issue, and a study by Zhu et al[62] investigated the effects of *Lactobacillus plantarum* JYLP-326 on this condition. The probiotic supplementation improved the symptoms of anxiety, depression, and insomnia, together with favorable changes in the patient's gut microbiota profile.

Psychosocial stress is a well-known risk factor for different mood disorders, including sleep disorders or depression[63]. *Bifidobacterium longum (BL) NCC3001* could have beneficial effects on stress-related symptoms, as shown by a recent study where healthy adults with mild-to-moderate stress received this probiotic therapy for 6 weeks, improving their sleep quality and reducing the perceived stress[64]. *Bifidobacterium breve* M-16V could also be effective in improving mood and sleep in patients with high anxiety levels, probably through the increase of pipecolic acid levels. This metabolite is involved in the GABA system and is known to be associated with beneficial effects on depression and anxiety symptoms[65].

Probiotic therapies could also be helpful in the management of neurological disorders, such as multiple sclerosis. In a randomized clinical trial by Asghari et al[66], *Saccharomyces boulardii* supplementation for 4 months reduced the inflammatory markers and the oxidative stress indicators while improving the quality of life, pain, and fatigue severity compared to placebo in MS patients.

CONCLUSIONS

During the past year, new data have consolidated the role of probiotics in the management of numerous disorders. As the field of microbiota modulation continues to develop, the use of probiotics and other therapeutic microbiome modulators is expected to gain a central role in the future of medicine. Nevertheless, high-quality and rigorous studies are necessary to further improve the efficacy and specificity of probiotic treatments.

Conflict of Interest

GI has received personal fees for acting as a speaker for Alfa Sigma, Biocodex, Illumina, Malesci, Sofar, and Tillotts Pharma and personal fees for acting as a consultant or advisor for Biocodex, Malesci, and Tillots Pharma. GC has received personal fees for acting as an advisor for Ferring Therapeutics. All other authors declare no competing interests.

Authors' Contributions

Writing - original draft preparation: M. Fiorani. Supervision: G. Ianiro, S. Porcari, S. Bibbò, G. Cammarota. All authors have read and agreed to the published version of the manuscript.

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ORCID ID

M. Fiorani: 0000-0001-7005-6147
S. Porcari: 0000-0003-0085-3954
S. Bibbò: 0000-0002-8043-4807
G. Cammarota: 0000-0002-8043-4807
G. Ianiro: 0000-0002-8318-0515

Ethics Statement

Not applicable due to the type of study.

AI Disclosure

The authors used no AI tools for the conceiving and writing of the manuscript.

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