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Review Article

Gut microbiota in human health: insights and discussion on the role of probiotics

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ABSTRACT

Gut microbiota remains stable and individualized throughout life, but there are inter-species or intra-species variations that may be controlled by various environmental factors. Several diseases may be associated with dysbiosis like inflammatory bowel disease (IBD), obesity, diabetes mellitus, irritable bowel syndrome (IBS), gastric and colon cancer, and sometimes colorectal polyps, non-alcoholic steatohepatitis (NASH), and liver cirrhosis, because of the gut-derived neurotoxins. There is a 10% to 30% risk of development of post-infectious IBS despite the beneficial effects of a low FODMAP diet on IBS symptoms. This diet reduces the luminal concentration of one of the most common bacteria that is the *Bifidobacterium*. Therefore, probiotics help in the restoration of normal gut microbiota, are a valuable tool in the treatment of certain diseases and help in recovering microbial balance in the gut. *Bifidobacterium* W11 is a novel probiotic with certain special characteristics that can be of benefit in dysbiosis. This review evaluates gut microbiota dysbiosis, associated complications of dysbiosis, and benefits of treatment with probiotics based on focused group discussions of various experts from India, followed by guidance statements based on analysis of published literature. The beneficial effects of *Bifidobacterium longum* W11 (*B. longum* W11) in the management of IBS, IBD, and liver diseases have been elaborated. The proposed management strategy can effectively aid the management of gut dysbiosis in several gastrointestinal conditions and help in understanding the judicious use of probiotics.

Keywords: Gut microbiota, Probiotics, IBS, IBD, *Bifidobacterium longum* W11

INTRODUCTION

The most colonized organ in the human body is the gastrointestinal (GI) tract consisting of trillions of organisms. The interplay of host-microbiome is required for maintaining a strong immune system, which allows the GI to remain healthy and free from pathogenic bacteria. Various environmental factors and host genetics influence the human gastrointestinal microbiome. Microbiota is the entire population of microorganisms including bacteria, fungi, archaea, viruses, and protozoans that live in the human body, and their collective genomes that form the human metagenome. The composition of gut microbiota varies between individuals and different GI segments; 10 to 1000 bacteria per mL are present in the gastric juice of the stomach; 10,000 to 10 million organisms per mL, in the jejunum; and more than a billion organisms per mL, in the colon. Thus, there is a total of 100 trillion bacteria within the body. These microbiotas influence many physiological processes in the body and impact the immune system. The predominant are *Bacteroidetes* and *Firmicutes*, while Actinobacteria and Proteobacteria are less frequently found. Firmicutes and Actinobacteria are generally considered as beneficial bacteria, and many of the Proteobacteria and *Bacteroidetes* can be pathogenic, particularly the Proteobacteria. Proteobacteria are more prevalent in the Asian and Indian populations and include pathogens like *Klebsiella* and *Enterobacter* as well as common diarrheal pathogens like *Vibrio cholerae* and *Salmonella*.[1,2]

The functions of the gut microbiota include fermenting non-digestible substrates like dietary fibers and endogenous intestinal mucus and supporting the growth of specialized microbes that produce short-chain fatty acids and gases. Gut microbiota also help in fermenting proteins like ammonia and phenols. They influence the host immune status and modulate systemic immunity-bacteria on the surface of the epithelium produce bacterial molecules that communicate with dendritic cells and the antigen-presenting cells. They influence the naïve T cells and differentiate them into Th1/Th2 effector cells that mediate inflammation; they can also influence T_{reg} cells that modulate and control inflammatory process.[1,2]

Foods can have beneficial effects on gut bacteria, or they can adversely modulate the microbiota load Probiotics and dietary fibers are generally beneficial, whereas saturated fatty acids and excessive protein intake can adversely modulate gut bacteria.[1,2]

EFFECTS OF DISTURBED GUT MICROBIOTA FLORA

The panel discussed eubiosis and the balance between good and aggressive or harmful bacteria. When the microbial balance is disturbed, it develops into a condition known as dysbiosis, which causes a reduction in bacterial diversity and leads to various complications. Various factors are responsible for imbalances in microbiota composition and functions: Proton pump inhibitors (PPIs) decrease normal gastric acidity and are one of the most misused drugs, particularly in India. Increase in stomach pH of due to PPIs leads to the growth of bacteria and disrupts the normal homeostasis of the gut microbial system.[3] Lack of judicious use of antibiotics disrupts the gut microbiota, and this may even result in permanent dysbiosis.[4] Increased production of trimethylamine N-oxide (TMAO) due to excessive red meat intake (L-carnitine is metabolized via trimethyl amine to form TMAO) and excessive overgrowth of the gut microbiota are responsible for excess deposition of cholesterol in vascular tissue that leads to development of atherosclerosis and cardiovascular or peripheral vascular diseases.[5] An exponential increase in autoinflammatory diseases in past half-century has led to dysbiosis-like states such as IBD, IBS, gastric and colon cancer, and sometimes colorectal polyps, NASH and liver cirrhosis. Neurodevelopmental disorders, cardiovascular disorders because of excess cholesterol deposition in the arterial walls, gallstones, diarrhea, constipation, malnutrition, and sometimes gut-derived neurotoxins may also be responsible. Mental stress, changes in dietary habits, or smoking and alcohol can also induce dysbiosis and cause subclinical inflammation in the gut and leaky mucosa that can impair intestinal permeability.[6,7]

INDICATIONS FOR THE USE OF PROBIOTICS[8]

Probiotics help in restoring microbial health in gastrointestinal diseases. They restore the normal gut microbiota by transplantation of foreign gut microbiota, a valuable tool in the treatment of certain diseases, which can help an individual in recovering gut microbial balance. *Bifidobacterium* and the *Lactobacillus* are the two bacteria that have significant beneficial effects in the management of active mild to moderate cases of ulcerative colitis; further, prebiotics like fructo-oligosaccharides are associated with early reduction in the fecal calprotectin in active ulcerative colitis. As per the world health organization, some probiotic strains may reduce pain and provide relief in IBS with a consistent reduction of abdominal bloating and flatulence.

IDEAL PROPERTIES OF PROBIOTICS

An ideal probiotic should be hydrolyzed or absorbed in the upper part of the gastrointestinal tract, should be a selective substrate for one or a limited number of bacterial commensals to the colon culture protagonist.[9]

It should be able to alter the colonic microflora towards a healthier composition or selectively stimulate the growth and/or activity of intestinal bacteria associated with health and well-being, should help in increasing the absorption of certain minerals such as calcium and magnesium, and it should have a favorable effect on the immune system and provide improved resistance against infections.[9]

USE OF PROBIOTICS IN VARIOUS GASTROINTESTINAL DISORDERS

Probiotics in IBS

Dysbiosis is a potential risk factor for IBS that causes abnormal intestinal immune activation and chronic gut inflammation. Low-grade mucosal inflammation in combination with visceral hypersensitivity and impaired bowel motility can be responsible for IBS pathogenesis. This may be a result of the compromised epithelial barrier, post-infectious alterations, dysbiosis, and altered stress levels that stimulate the aberrant immune system. Further, a history of infectious gastroenteritis induced by bacteria, parasites or viruses (referred to as post-infectious IBS) is also reported to cause dysbiosis.[10]

Another theory is when the gut bacteria ferment polysaccharides, gasses such as hydrogen and methane are generated as by-products. Additionally, the colon bacteria also produce short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, the SCFAs and gases of which could affect bowel movements as well as gut permeability.[10]

A study has shown that a lower abundance of butyrate-producing bacteria in patients with IBS, particularly in those with diarrhea-predominant IBS and IBS mixed type, may lead to impairment in intestinal permeability and activation of nociceptive sensory pathways, which can manifest in the symptoms observed.[11]

Patients with IBS not undergoing any therapy had a lower abundance of *Methanobacteria*.[11] Because methane production capacity is linked to low transit time and anti-inflammatory effects in the colon, a lower count of methanogens in patients with IBS reduces the ability for hydrogen gas removal from the colon, which may cause flatulence or excess gas in the abdomen.[10]

A meta-analysis has shown that in IBS, *Bifidobacterium* and *Faecalibacterium* were found to decrease, and the pathogenic *Bacteroides*, *Enterobacteriaceae*, and *Lactobacillus* communities were increased.[12] According to the World Gastroenterology Organization, some probiotic strains may reduce pain and provide relief in IBS with consistent reduction of abdominal bloating and flatulence in published trials.[13]

Probiotics were found to be statistically superior to placebo as per a recent meta-analysis promoted by the American College of Gastroenterology that evaluated 53 randomized controlled trials involving 5,545 IBS patients.[14] The experts prescribed probiotics for IBS, especially in diarrhea-predominant IBS. Probiotics are not used much in constipation-predominant IBS, but the literature regarding *B. longum* W11 shows its usefulness in constipation-predominant IBS. Experts concurred that diarrhea-predominant IBS responds well to probiotics along with rifaximin. A course of rifaximin is used for the first 2 weeks, and probiotics like *B. longum* W11 can be administered for four weeks thereafter; a good prognosis based on its properties and clinical experience has been observed with this regimen. A significant improvement in pain after the administration of probiotics containing *Bifidobacterium breve*, *Bifidobacterium longum*, or *Lactobacillus acidophilus* was reported.

Probiotics in non-alcoholic fatty liver disease

Dysbiosis can lead to increased intestinal permeability, promote translocation of commensal metabolites through the vascular system into the liver (endotoxemia), and directly contribute to hepatic lipid metabolism disruption and inflammatory processes in the liver.[15]

Insulin resistance is suggested to be the root cause and it can propel non-alcoholic fatty liver disease (NAFLD) and NASH. Gut microbiota influences insulin resistance, bile acid synthesis, and choline metabolism. Further, apart from a sedentary lifestyle, obesity and a high-fat diet too have a role in the progression of the disease. This causes microbial modification leading to endotoxemia and inflammation in the gut wall.[15]

Dietary habits may induce dysbiosis, which is characterized by an increased percentage of intestinal gram-negative bacteria, like proteobacteria that accelerates cholestatic liver fibrosis. Microbiota ferments carbohydrates to produce ethanol; this pathway is enhanced in the presence of obesity, diabetes, or chronic alcohol abuse or during excess intake of dietary carbohydrates leading to increase in gut dysmotility. The ethanol then reaches the liver via the portal vein and promotes steatosis, oxidative stress, and liver inflammation. Further, ethanol and its metabolic derivative acetaldehyde can also disrupt intestinal tight junctions and increase intestinal permeability. Therefore, modulating the gut microbiome can modulate the development of NAFLD, and the progression into NASH and hepatocellular carcinoma.[15]

Fecal microbiota transplantation (FMT) can be used to restore the gut microbiome, but reports have shown no significant change in the hepatic proton density fat fraction or the homeostasis model assessment-estimated insulin resistance (HOMA-IR) test after allogenic or autologous FMT. Allogenic FMT patients with elevated small intestinal permeability (>0.025 lactulose:mannitol) at baseline had a significant reduction 6 weeks after allogenic FMT. FMT does not have much effect on NAFLD, but it can improve gut permeability or strengthen the intestinal barrier, which can prevent entry of lipopolysaccharides (LPS) or endotoxins and elicit an indirect effect.[16]

The experts suggested that probiotics along with rifaximin is used in clinical practice for hepatic encephalopathy, and this regimen has shown improvement in psychometric score and ammonia levels. For minimal hepatic encephalopathy, rifaximin has been used for two weeks followed by one month of probiotics, and it found to cause improvement along with lactulose.[17]

Probiotics can decrease serum ammonia and endotoxin levels, improve symptoms of minimal hepatic encephalopathy, and prevent overt hepatic encephalopathy development in patients with liver cirrhosis.[18]

Benefit of probiotics in patients with NASH is still under evaluation, but they can be used as adjuvant therapy for an indefinite duration because NASH itself is not a curable disease. Lifestyle modification is the single most important factor for the correction of metabolic abnormalities in NASH. Similarly, in patients with hepatic encephalopathy due to chronic liver disease, which is a non-reversible condition, if probiotics are effective, then they should be used for an indefinite period, for the benefit to be persistent.[19]

Probiotics in IBD

Intestinal dysbiosis is a potentially relevant mechanism underlying IBD pathogenesis, comprising of regions with high loads of bacteria that are correlated with a greater incidence of Crohn's disease and ulcerative colitis, particularly in the terminal ileum and the colon. Colonic inflammation and IBD are linked to the gut microbiome. Different facultative anaerobes like Proteobacteria are increased, whereas *Clostridia* and *Bacteroides* are

decreased, resulting in less diversity of the gut microbiome. An increase in the cell counts of fungi like *Candida* and some bacteriophages leads to upregulation of the proinflammatory pathways and production of oxidative stress that favor the development of these facultative anaerobes and decrease biodiversity. Changes in microbiome related to IBD is a condition with decrease in alpha diversity. There is a decrease in Bacteroides *and Firmicutes*, an increase in proteobacteria and gram-negative bacteria like *Escherichia coli*, and *Faecalibacterium prausnitzii* and a decrease in the *Clostridia, Ruminococcus*, and *Bifidobacteria*.[20]

The experts mentioned that probiotics are rarely used for the induction of remission or as a measure to maintain remission in IBD, but they may be used as an adjuvant treatment. For patients with IBD refractory to immunomodulators or biologicals, FMT has shown promising results. FMT can be an add-on or an experimental therapy. An IBD MED India study with Israel conducted in healthy volunteers and patients with early Crohn's disease showed that exclusion diet alone was effective in inducing or maintenance of remission in patients with mild to moderate disease who were on stable doses of other drugs.

The experts proposed probiotics to have a role in IBD treatment, where most patients are administered probiotics along with immunomodulators. The reason for including probiotics being to decrease the levels of proinflammatory cytokines. Hence, all patients with Crohn's disease or ulcerative colitis should be put on probiotics. A large multicenter study from Northern India showed that multiple strain probiotics can induce remission in mild to moderate ulcerative colitis. Therefore, prescribing probiotics to Indian patients would not be detrimental because rapid westernization in India is indeed resulting in changes to bacterial flora within the gastrointestinal tract of Indian patients.

Bifidobacterium Longum W11: A novel probiotic

Bifidobacterium W11 is a novel probiotic that includes three subspecies *B. longum*, *B. infantis*, and *B. suis*. *Bifidobacterium longum* w11 can tolerate low pH and is resistant to bile salts, which allows survival in the intestine. It is an efficient colonizer, it can be easily taken orally, and it can pass through the intestine where it colonizes and stabilizes the intestinal mucosal barrier. It excludes pathogenic bacteria, has immune modulator activity, and is an antibiotic-resistant organism. Compared to other capsules used with multi strains *Bifidobacterium longum* w11 requires once-a-day dosing and no storage requirement.[21]

The antibiotic resistance of *B. longum* W11, especially resistance to rifaximin, is a very important feature when compared to other probiotics. This characteristic is chromosomally based and hence not transferable from one bacterium to another. The bacterium is not harmful to the intestine and can be safely used in combination with a regimen because of its antibiotic-resistant property; hence, it is helpful in curing dysbiosis.[21]

B. longum W11 was observed to be resistant to various commonly used antibiotics that are administered to patients with IBS or intestinal bacterial overgrowth associated with IBS, such as rifampicin, rifapentine, rifabutin, and rifaximin at the concentrations ranging from 32 to 256 mg/mL.[21]

Bifidobacterium longum W11 in IBS

A study was conducted to evaluate the efficacy of rifaximin alone or in association with the probiotic strain of *B. longum* W11 in reducing symptoms in patients with IBS. Patients treated with rifaximin 200 (2 capsules two times a day [bid] for 10 days in a month) followed by a formulation of the probiotic strain of *B. longum* W11 (one granulated suspension for 6 days on alternate weeks) reported a greater improvement of symptoms compared with patients receiving only rifaximin 200 (2 capsules bid for ten days in a month). The increased colonization by *B. longum* W11 eradicates the bacterial overgrowth of the small intestine and reduces symptoms, especially those related to bowel habits and stool frequency in patients with IBS after the cyclic administration of rifaximin.[22]

In patients with IBS and functional constipation, use of fructo-oligosaccharides and *B. longum* has shown to improve complete spontaneous bowel evacuations and consistency of stools, and overall feeling of well-being. It was effective in relieving both abdominal constipation and pain and distinction and bloating in these patients.[23]

Experts suggested that in patients with IBS, *Bifidobacterium* and *Lactobacillus* species and sometimes a mixture of both constantly showed beneficial effects in all the studies. Thus, probiotics should be administered for a long time, with recent data showing that even 8-week dosing would be sufficient.

B. longum W11 in liver diseases

Studies conducted to assess clinical efficacy of *B. longum* W11 with fructo-oligosaccharides in treatment of minimal hepatic encephalopathy. Significantly greater efficacy observed in reducing plasma ammonia levels and improving neuropsychological tests when compared with placebo.[24]

When *B. longum* W11 + lifestyle modification was compared with lifestyle modification alone in patients with NASH, a statistically significant change was observed in parameters like liver enzymes, C-reactive proteins, tumor necrosis factor (TNF)-α, HOMA-IR and serum endotoxins.[25]

Rifaximin is a treatment modality that has been established for hepatic encephalopathy. If *B. longum* is

added to the resistant rifaximin and rifampicin group of antibiotics, it works well as an adjunctive therapy with rifaximin in the setting of hepatic encephalopathy.[26]

In NAFLD, theoretically, because of the decrease in the number of *Bifidobacteria*, there are increased plasma LPS levels that increase the inflammatory cytokines.[27]

With the supplementation of good bacteria like *B. longum* W11 along with prebiotics, inflammation can be decreased. Reports have shown that lifestyle modification is the best treatment for NAFLD. *B. longum* with lifestyle modification led to a significant improvement in liver function tests, liver steatosis, liver stiffness, and dyslipidemia versus lifestyle modification alone.[28]

Experts agreed that they used this *Bifidobacterium* sometimes in chronic persistent hepatic encephalopathy where patients failed to respond to rifaximin.

B. longum in IBD

Various studies have shown that *B. longum* can improve the clinical symptoms of patients with mild to moderately active ulcerative colitis; the disease activity and clinical scores were greatly reduced at 8-weeks versus the placebo-treated group. Another study demonstrated that *B. longum* used together with a prebiotic synergy, reduced Crohn's disease activity and histological score. Further, *B. longum* and inulin-oligofructose administered in patients with ulcerative colitis for 4 weeks decreased the expression of β-defensin, IL-1α, and TNF-α genes, and improved the rectal biopsy, inflammation, and regeneration of epithelial tissue.[29]

Experts concluded that probiotics can be effective, especially when used in situations where disorders are chronic, and where there is no effective definitive treatment. It is usually subjective at this stage and based on the experience of practicing physicians. Rifaximin is used for a variety of gastrointestinal conditions, and a probiotic can be safely used with it. Following the course of rifaximin, a course of probiotics for about four weeks can be used, which is a major advantage for *B. longum* W11 strain.

CONCLUSION

Gut microbiota influences many physiological processes and the immune system. They ferment non-digestible substrates like dietary fibers and endogenous intestinal mucus, supporting the growth of specialized microbes. They also control glucose metabolism and help in gut signaling to the brain. Disturbed microbial balance develops into a condition known as dysbiosis, which causes a reduction in the diversity of the bacteria and leads to various complications. Probiotics help in restoring microbial health in several gastrointestinal diseases. *Bifidobacterium* and *lactobacillus* species have significant beneficial effects in the management of active mild to moderate cases of ulcerative colitis; further, prebiotics like fructo-oligosaccharides cause early reduction in fecal calprotectin in active ulcerative colitis. Probiotics are also beneficial in IBS-D when used in combination with rifaximin. Probiotics reduce pain and provide global relief in IBS, with a consistent reduction of abdominal bloating and flatulence. Probiotics can also decrease endotoxin levels, improve minimal hepatic encephalopathy, and prevent overt hepatic encephalopathy development in patients with liver cirrhosis. Their use in NASH is still experimental.

B. longum W11 is a novel probiotic with several beneficial characteristics such as tolerance to low pH, resistance to bile salts, efficient colonization, stabilization of the intestinal mucosal barrier, exclusion of pathogenic bacteria, and immunomodulatory activity. It is an antibiotic-resistant organism that requires once-a-day dosing. *B. longum* W11 can be beneficial in hepatic encephalopathy along with rifaximin by improving psychometric score and ammonia levels. Its combination with rifaximin 200 showed greater improvement of symptoms compared with rifaximin 200 therapy alone. It is effective in relieving both abdominal constipation and pain and bloating in patients with IBS. *B. longum* W11 with fructo-oligosaccharides can significantly reduce plasma ammonia levels and improve neuropsychological tests in patients with minimal hepatic encephalopathy. *B. longum* improves symptoms and reduces disease activity by decreasing the expression of proinflammatory genes in patients with ulcerative colitis and Crohn's disease. Thus, probiotics can be effective, especially when used in situations where the disorders are chronic, and where there is no effective definitive treatment, with *B. longum* W11 being a preferred strain due to multiple advantages.

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