5 Probiotics as Anti-Inflammatory Agents in Inflammatory Bowel Disease and Irritable Bowel Syndrome

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Abstract

Studies involving manipulation of intestinal microflora with probiotic species have suggested potential effectiveness in multiple gastrointestinal diseases including inflammatory bowel diseases. Resulting benefits of probiotics include competitively excluding pathogens, improvement of mucosal barrier function, and hence maintaining the gut homeostasis and modulating the immune system by inducing the release of cytokines. Few lactobacillus strains are also known to modulate the perception of pain by inducing effects similar to that of morphine in the intestinal epithelial cells. Probiotic products like VSL#3 (*Bifidobacterium longum*, *B. breve*, *B. infantis*, *Lactobacillus plantarum*, *L. acidophilus*, *L. paracasei*, *L. bulgaricus*, *Streptococcus thermophilus*), Culturelle (*L. rhamnosus* GG), Florastor (*S. boulardii*), Align (*B. infantis*), DanActive (*L. casei*), Mutaflor (*E. coli* Nissle 1917) are current examples of treatments. Probiotics are also increasingly being added in dairy as well as non-dairy products like drinks, yoghurts, etc. Most studies regarding the anti-inflammatory effects of probiotics are preliminary and seem promising but require further clinical trials. There is also scope for studies on the dosage, duration of therapies, ways of administration, and strain combinations.

Keywords

Anti-inflammatory probiotics · Inflammatory bowel disease · Irritable bowel syndrome · Ulcerative colitis · Gut microbiota

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5.1 Introduction

Inflammatory bowel diseases (IBD) cause different forms of inflammation in both the small intestine and colon. More than five million people have been reported to be affected worldwide, by IBD. IBD include chronic immune-mediated gastrointestinal disorders, mainly Crohn's disease (CD) and ulcerative colitis (UC). Although the exact causes of these diseases are unknown, most experts hypothesize that complex inflammatory response to environmental triggers results in IBD. Growing evidence suggests that, when the dynamic equilibrium of gut bacteria and mechanisms for defense in the host, at the intestinal mucosa (dysbiosis) gets disrupted, it may set off an inflammation reaction. Gastrointestinal tract beginning from the oral cavity and ending at anus is affected in Crohn's disease, whereas in case of ulcerative colitis, the large intestine and rectum are affected. Figure 5.1 represents the triggering factors for IBD.

When the difference between CD and UC with the help of absence of standard golden test becomes difficult, the third type of inflammation of the bowel is believed to have emerged which is known as inflammatory bowel disease unclassified or alternatively indeterminate colitis (IC). IBD is the most common between 15 and 40 years age group, although it can affect people of any age. Among patients

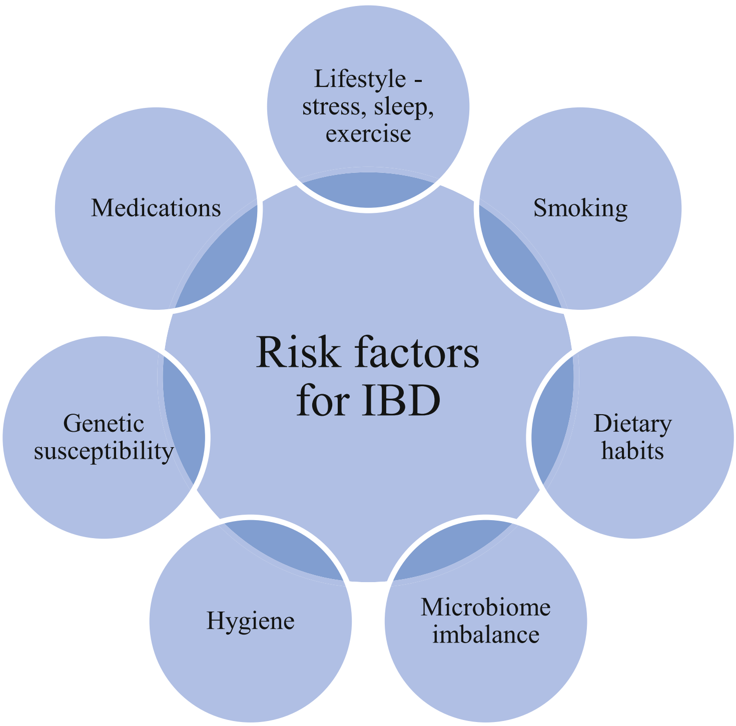

Fig. 5.1 Risk factors for IBD

Table 5.1 Difference between ulcerative colitis and Crohn's disease

Ulcerative colitis	Crohn's disease
First case reported in Europe in the year 1875	First case reported in the USA in the year 1932
Affects primarily colon	Affects various GI sites
Continuous inflammation of colon	Healthy and inflamed areas mixed
Affects innermost lining of colon	Can affect all layers of the bowel wall

suffering from IBD, about 7–20% are children and about 65–80% are people below 40 years of age. UC occurs at later years of life in people who smoke compared to patients who don't (Mahdi 2018). Table 5.1 shows the differences between ulcerative colitis and Crohn's disease.

Conventional treatments employed for IBD target inflammation and focus on suppressing the enhanced immune response with antitumor necrosis factor antibodies, steroids, and thiopurines. However, these treatments may result in serious and adverse health effects linked with chronic suppression of the immune response. Therefore, a better understanding of the pathophysiology of the disease has helped to propose alternative therapies by investigators, which focus on restoring the balance of the gut microbiota and eliminate bacterial antigens (Veerappan et al. 2012).

Irritable bowel syndrome, however, is a functional condition of the bowel in which individuals suffering experience altered bowel habits, abdominal pain with either diarrhea and/or constipation. It is diagnosed clinically as no biomarker has been found till date (Canavan et al. 2014).

5.2 Gut Microbiota

A dynamic and metabolically active ecosystem, the gut microbiota, serves a crucial functioning well-being and health. As revealed by researches on genotypic sequencing it has been demonstrated that the human gut can harbor between any of 1000 and 1150 varied species, with persons having at least 160. However, of these, 18 species were found in all participants of the study and 57 species were present in 90% of the participants, showing substantial dominance and stability between different individuals, of these microbes across humans (Zhu et al. 2010). Several factors such as age, disease, and food habits have an effect on the constitution of the gut microbiota. Alteration in the gut microbiota composition such as an increase in the levels of pathogenic bacteria and reduced levels of *Lactobacilli* and *Bifidobacteria* is associated with a range of gastrointestinal disorders (Guarner et al. 2012; Panghal et al. 2018). The human microbiota undergoes several changes depending upon the diet, environmental factors, use of medication, and intestinal transit time; however, it demonstrates a tendency to restore to the original composition, a phenomenon termed as resilience (Caporaso et al. 2012). A research study carried out using molecular biology techniques, with adults from Europe, Japan, and North America revealed that the composition of the gut microbiota is constituted predominantly by

3 "enterotypes," recognized by variation in the population of *Bacteroides* spp. (enterotype 1), *Prevotella* spp. (enterotype 2), and *Ruminococcus* spp. (enterotype 3) (Arumugam et al. 2011). Host immune response is largely affected by the gut microflora and therefore, manipulation of the composition of gut microbiota can help in amelioration of these gastrointestinal disorders (Celiberto et al. 2017).

5.3 Probiotics

Probiotics are microorganisms that provide beneficial and desired impacts on human health. The Food and Agriculture Organization of the WHO has defined a probiotic as "a live organism that, when ingested in adequate amounts, exerts a health benefit to the host." The microorganisms commonly used as probiotics are *Lactobacilli*, *Bifidobacteria,* and non-pathogenic yeasts such as *Saccharomyces boulardii*. Essential requirements for these microbes are that they should carry the ability to survive low pH due to stomach acid and bile and maintain the viable counts through the storage period and importantly should be safe for human consumption as depicted in Fig. 5.2 (Vasudha and Mishra 2013).

Fuller used the term "probiotic" for the first time and described it as "a live microbial feed supplement which beneficially affects the host animal by improving its microbial balance." Marteau et al. (2002) defined probiotics as "microbial cell preparations or components of microbial cells that have a beneficial effect on the health and wellbeing." Several mechanisms explain the beneficial action of probiotics for positively affecting the host. Probiotics prevent as well as ameliorate the condition in inflammation, by affecting the host immune response. Probiotic bacteria dwell at the binding sites of the gut mucosa and hence prevent the pathogens from adhering to it. *Lactobacilli* also secrete some proteinaceous compounds, such as bacteriocins, which work as local antibiotics in opposition to many pathogens and also thereby decreasing the production of pro-inflammatory cytokines. IgA is produced and is also stimulated by probiotics. *Lactobacilli* cause inhibition in the growth of bacterial pathogens by producing lactic and acetic acid. Probiotics also compete with the pathogens for nutrients and therefore, modify toxins that are produced by the pathogens found in the gut. It has been demonstrated that specific

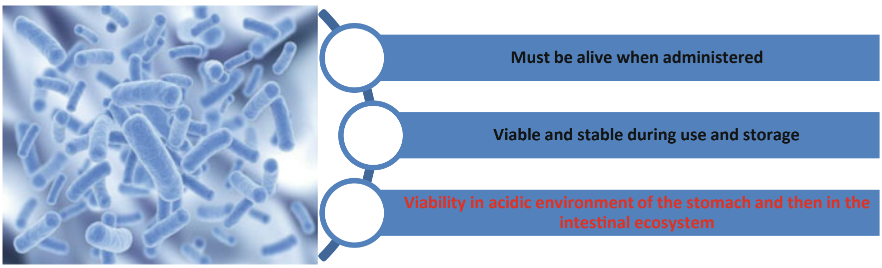

Fig. 5.2 Probiotics according to World Health Organization

DNA extracted from probiotics (VSL #3) could reduce the experimental colitis in animals (Chermesh and Eliakim 2006).

A precondition for probiotics to be used is its efficacy and safety. The characteristics for efficacy of probiotics are resistance to the process of digestion, by enteric enzymes, bile and gastric acids, and pancreatic enzymes, and the ability of preventing the pathogen binding, adherence, and multiplication of pathogens inside the gastrointestinal tract. Many types of bacteria qualify as probiotics such as lactobacillus family, but all bacteria cause different types of actions in different forms of diseases, some of the diseases can be better treated with combinations of these bacteria and their dosing is also an issue. Hence, probiotic treatment can be considered relatively safe but not as completely risk free (Chermesh and Eliakim 2006).

5.4 Pathophysiology of the Disease

5.4.1 Inflammatory Bowel Disease

Normal mucosal integrity is disrupted due to inflammation anywhere in the gastrointestinal tract. Therefore, IBD is very painful and can be potentially fatal in several cases. The symptoms include pain in the abdomen with cramps and swelling in stomach, bloody diarrhea, fatigue, fever, weight loss, vomiting, and anemia. Other symptoms which are sometimes seen include pain in the joints, red and painful eyes, skin nodules, and jaundice. These symptoms relapse characteristically (Mahdi 2018). Recent studies implicate that an imbalance of the gastrointestinal microbiome can be a potential trigger in case of IBD. Use of probiotics as a supplement alongside standard anti-inflammatory therapy is gaining interest and popularity. Potential mechanisms of action using animal models suggested that probiotics can reduce inflammation in the colon.

Distinct differences exist in the histopathology of the two main types of IBD: Crohn's disease and ulcerative colitis. The whole intestinal segment is affected, interspersed with some healthy areas in the case of CD and this is a case of chronic inflammation. The terminal ileum and colon are affected in most cases and it begins with short duration of intense occurrence of diarrhea, fever, weight loss, and repeated abdominal pain. Whereas, in ulcerative colitis, the inflammatory reaction demonstrates distinct characteristics such as the occurrence of abscesses in the crypts and permeation of eosinophils, neutrophils, and plasma cells that attack the lining of the colon and rectum repetitively. Common symptoms in the case of individuals suffering from UC are diarrhea, bleeding from rectum, mucous discharge, and abdominal pain. Figure 5.3 shows images of affected areas of the human body in the case of Crohn's disease and ulcerative colitis.

People of all age groups are affected by IBD; however, a higher chance of occurrence is observed in people between 15 and 30 years of age and elderly population. Several systematic scientific investigations in the past few years have revealed an increased incidence of IBD among nations where the socio-economic status is on the rise (Celiberto et al. 2017).

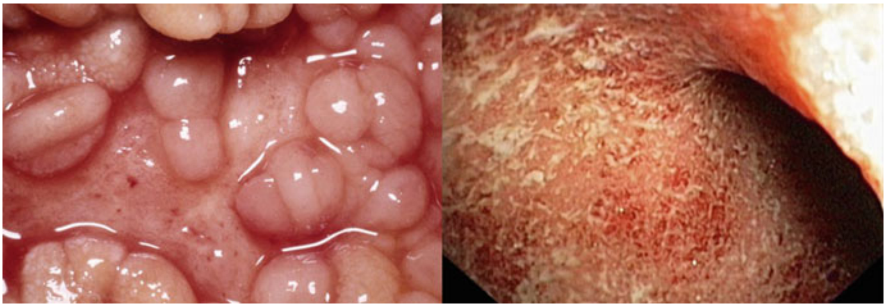

Fig. 5.3 Areas affected by (1) Crohn's disease and (2) ulcerative colitis [Source: https://www.webmd.com/ibd-crohns-disease/ss/slideshow-inflammatory-bowel-overview]

Probiotics play a role in immunomodulation and anti-inflammatory response and are used in the treatment of chronic diseases. A study by Mack (2011) conducted a systematic review on the outcomes of consumption of probiotics on chronic intestinal diseases occurring in animals and humans. Probiotic strains decreased the expression of pro-inflammatory cytokines through a mechanism which is chiefly mediated by toll-like receptors. Probiotics' administration bettered the condition of the disease and the histological changes in maximum animal studies, but few results also suggested that care needs to be exercised when probiotics are administered, in cases of relapse of IBD. Probiotic supplementation seems to have potential and is safe for individuals suffering with UC and CD. Clinical symptoms were improved by the use of *Bifidobacterium longum* 536 in patients suffering from mild and moderate UC (Mack 2011).

Although the data present is not enough to recommend probiotics for remission in UC and CD, there is enough evidence that supports that probiotics can be employed for diminution of severity in pouchitis. The regulatory standards for probiotics are insufficient but probiotics have minimal side effects according to reports and are hence relatively safe. A higher number of in-depth studies are required for supporting the efficacy and safety of these, before they can be used as treatment in IBD. Figure 5.4 represents the mechanism of symptoms in IBD and IBS (Spiller and Major 2016).

5.4.2 Irritable Bowel Syndrome

Bloating, abdominal pain, and a change in the stool frequency are symptoms observed in the case of irritable bowel syndrome. It is a challenging illness which results in a deteriorated quality of life. The prevalence of IBS is between 10 and 20% in developed nations, and increased absence and excessive utilization of healthcare services result in insignificant economic consequences. Many factors such as genetics, gastrointestinal microbiota, behavioral pathways, and abnormal pain processing serve a crucial role in pathogenesis of the disease. A large case controlled research

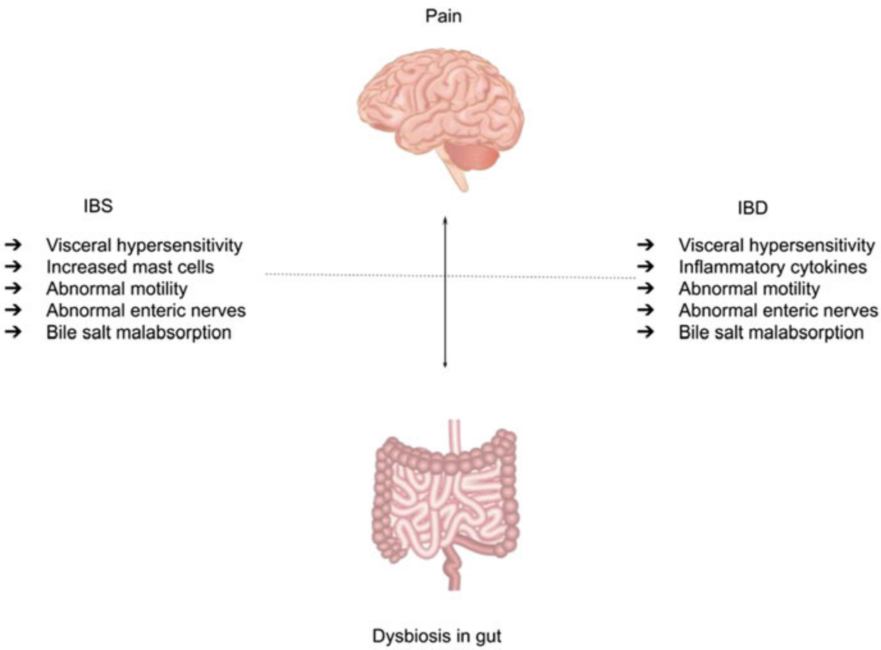

Fig. 5.4 Mechanism of symptoms in IBS and IBD

revealed that infectious gastroenteritis resulted in almost four times increase in the chances of developing irritable bowel syndrome within the following 2 years (Whelan and Quigley 2013). Many researches have informed a luminal dysbiosis in IBS, with many patients showing decreased counts of *Lactobacilli* and *Bifidobacterium*; these microbes are generally used in probiotic products.

5.5 Probiotics: Mechanisms of Action

Probiotics include a few symbiotic bacterial flora, having beneficial effects on host health and also prevent disease or help in its treatment. Probiotics have shown beneficial effects on several human diseases such as inflammatory bowel diseases (IBD), during clinical trials. However, clearly understanding and establishing the mechanism of action is an important matter related to the usage of probiotics clinically.

5.5.1 Inflammatory Bowel Disease

Essentially, research studies highlight three different molecular and cellular mechanisms for regulation of probiotic therapy in IBD, as discussed below:

(a) Bactericidal substances are produced by probiotics, which obstructs the effects of pathogenic bacteria and causes competitive inhibition in case of the pathogens and toxins in their ability to adhere to the intestinal epithelium;
(b) Immune responses can be regulated by probiotics by improving the intrinsic immunity and modifying inflammation induced by pathogens via signaling pathways that are regulated by receptors; and.
(c) Probiotics improve intestinal epithelial homeostasis by enhancing cell survival in intestinal epithelium, stimulating defense responses and improving barrier function. Probiotics regulate host cell by signaling pathways, including mitogen-activated protein kinases, Akt and nuclear factor-κB to arbitrate the role of the intestinal epithelium.

Developing an understanding of the mechanism of probiotic action will help in forming the rationale, in support of further studies, with new hypothesis to explain the clinical effectiveness in preventive and alternative treatments in case of IBD (Ng et al. 2008).

5.5.2 Irritable Bowel Syndrome

Many studies point towards the positive health effects of probiotics in IBS. First and foremost, numerous probiotic microorganisms exhibit antiviral and antibacterial effects and could therefore check or alter the path of IBS, postinfection. Moreover, probiotics have been successfully demonstrated to exhibit anti-inflammatory effects at surface of mucosal membrane; by decreasing its inflammation, probiotics can reduce immune-mediated activation of enteric motor and sensory neurons and modify the patterns of nerve activity between the gut and the central nervous system. Third, possible mechanism of action of probiotics could be by modifying the composition of the gastrointestinal microflora (Oelschlaeger 2010). The position of gut flora in IBS is still a point of disagreement and lacks consensus; however, probiotic-related variation in the intestinal microflora could straight away (via the escalation of commensals, i.e., *Lactobacilli* or *Bifidobacteria*, or the exclusion of disease causing microbes) or in turn (by way of reducing either pathogen-related inflammation or bacterial fermentation) affect the functioning of the gut. Lastly, probiotics could modify the composition and/or volume of stool and gas or cause an increased intestinal mucus secretion; effects that could influence the handling of its contents in the intestine and thus transform symptoms such as diarrhea and constipation.

5.6 Biological Basis for Positive Action of Probiotics

Biological effects of probiotics that may help in amelioration of condition in inflammatory bowel disease and irritable bowel syndrome can be categorized as follows:

5.6.1 Pathogen Resistance

Probiotics are believed to maintain host–microbial homeostasis and therefore reduce attack by pathogens and their increased presence in the gut. If endogenic microorganisms inhabit all functional niches, the pathogenic invasion can be reduced. Probiotics can prevent opportunistic infection either by occupying functional niches which are exposed by internally originating community or they might modulate the environment by secreting short chain fatty acids (SCFAs), bacteriocins, reactive oxygen species, and lactic acid, thereby inhibiting the growth of pathogens.

5.6.2 Nutritional Process

Some species in the gut microbes contribute to availability of vitamin and produce SCFAs. Gut microorganisms can produce vitamin K and B_{12}, biotin, pyridoxine, folate, thiamine, and nicotinic acid. Also, butyrate is a major source of energy and also maintains the enteric mucosa.

5.6.3 Immune Process

Probiotics have been proved to have a number of positive effects on the immune system. Some probiotics are known to be immunostimulatory, they induce IL-12 and NK or natural killer. Some species are anti-inflammatory and induce IL-10 and regulatory T cell pathways. Specific probiotic strains have specific effects on the immune system, some act as immunostimulatory and some as anti-inflammatory agents.

5.6.4 Rectifying Contaminants

Some probiotics such as *Pediococcus pentosaceus* are known to lower the risk from intake of compounds that are hazardous. It disintegrates fumonisins that are a group of mycotoxins which are produced from fungi, *Fusarium* spp.

5.6.5 Drug Metabolism

Gut microbiota can play a pivotal part in metabolism of drugs that can consequently, positively impact the therapy for various disease conditions. Competitive inhibition of hepatic sulfotransferases can decrease the liver's capacity to metabolize paracetamol; however, gut microbiota may play a crucial role in its metabolism (Li et al. 2016). Moreover, there is a lot of evidence to prove that environmental chemical pollutants as well as dietary ones can interfere with functions of gut bacteria such as transcription and metabolism, which can lead to an adverse effect on the host health, by inducing an immunostimulatory reaction inside the gastrointestinal system.

5.6.6 Bile Acid Metabolism

Deconjugation of primary bile acids and their conversion to secondary bile acids by some species of microbes in the gut like *Bacteroides intestinalis* are known. Secondary bile acids then hinder the germination of *Clostridium difficile* spores and hence restrict the increase of *C. difficile* (Day et al. 2019).

5.7 Microbiology Based Theories

Probiotics are considered to be safe as food additives, nutritional supplements, or pharmaceutical formulations. Studies suggest that dead microorganisms and their biologically active compounds play protective functions as well and therefore, the definition of "probiotic" should be revised or there should be implementation of classifications. Specific microbial strains have different mechanisms of action. Growth factors are produced by probiotic strains which help in strengthening the gut epithelium and antimicrobial substances such as SCFAs, hydroperoxides, bacteriocins, lactic and bile acids that help in killing harmful microorganisms. Consequently, cellular components get released inside the gut; this enhances the production of pro-inflammatory cytokines and activates immune responses and synthesis of immunoglobulin. It also improves lymphocytes and macrophage activity. Although immune tolerance is a plausible consequence of these improvements, there is little or no agreement in this regard. Benefits of probiotics other than immune improvements are improvement in the process of digestion and absorption, pH alterations, amalgamation of pathogens, and isolation of metabolic toxins. Animal models as well as in vitro assays suggest that decrease in apoptosis can also be achieved by probiotics along with increase in mucus synthesis, repair of tissues, and creation of tight linkages in epithelial cells in the gut, hence causing reduction in the permeability of intestine and enhancement of the barrier functions and its protection. *Lactobacillus* species (e.g., *L. rhamnosus*, *L. casei*, *L. plantarum*, *L. paracasei*, *L. acidophilus*, *L. johnsonii*, *L. reuteri*, *L. gasseri*) and Bifidobacterium (e.g., *B. bifidum, B. longum, B. infantis, B. animalis, B. lactis, B. breve, and B. adolescentis*) are the most commonly used probiotic strains in formulations, but an approach with combining the species is also being applied increasingly. Other strains that are used are Streptococcus spp., *Enterococcus* spp., *Lactococcus* spp., *Clostridium* spp., and non-pathogenic *Escherichia coli*. New genera of bacteria and species have also shown good insightful information in preclinical trials. New-generation probiotics is the name given to these bacteria. They are more complex than common probiotics in an effort to imitate fecal microbiota transplant treatments. These probiotics of the new generation include Clostridium clusters IV, XIVa, and XVIII, *Akkermansia muciniphila*, *Bacteroides uniformis*, *Eubacterium* *hallii, B. fragilis,* and *F. prausnitzii*. Current challenges in the way of employing these new-generation microbes as probiotics are technological aspects. Clostridium clusters XIVa and IV boost the Treg differentiation process, which is significant in case of immune tolerance. Indeed, in the gut of IBD patients, these bacteria are decreased and Tregs are increased, the expansion is still insufficient in restraining the development of inflammation. Gastrointestinal microbiota does not only include bacteria, some studies suggest use of yeasts in their formulations as probiotics along with bacteria and even as single-drug formulation. *Saccharomyces boulardii* has many anti-inflammatory properties and is the most commonly used strain in this context (Basso et al. 2018).

5.8 Probiotics for Treatment of Gastrointestinal Diseases

The global market is continuously expanding in case of probiotic supplements. Although the public perceives probiotics as beneficial, the studies to conclude that probiotic strains can improve characteristics of disease are few. There is a lack of research trials on a larger scale and the understanding of the reciprocal action with the human system after supplementing with probiotics. For probiotics to render to routine healthcare more in-depth research of various strains individually and their response to application of advanced measurement techniques is required. This will provide useful data or use of probiotics in routine healthcare practice.

Health claims need to be specific in case of probiotics and European Food Safety Authority (EFSA) considers claims like "strengthens the immune system" to be too vague. A lot of research has gone into making a base of evidence that probiotics can have an impact on different biomarkers. For a clearly displayed cause and effect relationship at the minimum randomized, placebo-controlled clinical trials are required by EFSA. Research and development lacking in investment and fundamental knowledge and having a poor design of study leads to "pilotitis"—where small projects create insufficient evidence for regulatory approval. An example is the systematic study of randomized controlled trials which investigated effects of probiotics, in remission of IBS. 35 RCTs were reviewed, out of those 3 had minimum 100 participants, it was deduced that about 75% were just preliminary studies (Dignass et al. 2012).

Appropriately driven phase III clinical trials for probiotics are needed to establish and improve confidence in efficacy of product for clinicians and therapists (Basso et al. 2018).

5.8.1 Probiotics in IBS

Irritable bowel syndrome (IBS) is highly prevalent and affects about 3 to 15% of the general population. Its characteristics include unexplained pain in the abdomen, bloating, and discomfort along with changed bowel habits. Multiple causes have been discovered in pathophysiology of inflammatory bowel diseases. Along with abnormal gastrointestinal motor function, it has been linked with visceral hypersensitivity, inflammation, autonomic dysfunction, and even psychosocial factors. According to a study, IBS developed in a subgroup of patients after an acute bacterial infection in the bowel. Inflammatory cells like the mast cells and lymphocytes in the mucosa of colon were found to have increased in IBS patients which suggested that these patients had an ongoing state of inflammation (Bennet et al. 2015). Probiotics can be beneficial in postinfectious IBS since they have shown to benefit in acute cases of inflammatory bowel disease as well as infectious diarrhea. Another reason in favor of using probiotics is that they can influence the process of fermentation and avoid gas production by changing the flora in the colon. Although there is less data to support the benefits of probiotic treatment in controlled clinical trials, still there is enough to support that they can normalize the levels of inflammatory cytokines and other symptoms of IBS. The comparison between various studies is complicated since the sample sizes are different and so are the probiotic bacteria used. Though the preliminary results look promising, the clinical efficiency and the precise mechanism of action in inflammatory bowel syndrome are to be studied with better designed experiments and controlled trials (Andresen and Baumgart 2006).

5.8.2 Probiotics in IBD

As mentioned earlier, ulcerative colitis and Crohn's disease are the two main types of inflammatory bowel diseases (IBD).

These are diseases of the gastrointestinal tract which are characterized by chronic inflammation. An imbalance between the intestinal mucosa and the commensal gut flora related to the immune system is the prime reason studied in the pathological process resulting in the development of these diseases. Theory suggests that probiotics can be utilized to treat IBD as they can interfere with the abnormal homeostasis that is a characteristic of IBD. They can hence reestablish the immune-bacterial interaction in the mucosa of the intestine. The mechanism of action includes reconstituting the composition of flora that is altered in case of IBD. They also help in enhancing the epithelial barrier's integrity. They promote the tolerance action by the accessory cells or the antigen-presenting cells along with strengthening the defense mechanism of the inborn immunity and suppression of adaptable immune responses that are capable of inflammation. There is not enough positive clinical evidence that supports the experimental evidence regarding the benefits of probiotics in IBD. Diversity of microorganisms that have been used for various trials and the varied dosages due to lack of standardization could be the reason for the discrepancies. Also, the scheme of administering the probiotics was different. The varied clinical phenotypes and the heterogeneity in the clinical trials are the important critical issues for the use of probiotic therapies optimally in case of patients suffering with IBD (Pagnini et al. 2013).

The number of randomized trials for consequence of probiotics is limited, in case of remission in ulcerative colitis and there are many differences in their methodology. The studies that exist until now have been about comparison of probiotics with anti-inflammatory drugs. These studies suggest that the efficacy and safety of the two are comparable. An alternative is using the probiotics that cure inflammation by interacting with the host epithelium. The microfloral composition as well as metabolic activities can be modified using probiotics as they can prevent the growth of potential pathogens. Pathogenic bacteria are linked with inflammation. Rigorous research is needed in the complex field of probiotics. If bacteria contribute to the pathogenesis of ulcerative colitis and resistance to antibiotics, probiotics can offer a substitute mechanism to manipulate the microflora in continually occurring diseases. Many studies suggest that some selected probiotic preparations have a positive influence on gastrointestinal diseases including UC. The most widely used probiotics in humans are *Bifidobacteria* and *Lactobacilli*. However, information is based on relatively small studies, which are insufficient to establish if they are definitely useful, and the pros and cons implicated are still feebly comprehended.

There have been reports suggesting significant improvement with different strains in bacterial species and yeasts. As mentioned by Zigra et al. (2007) "studies regarding *Bifidobacteria* treatment in a control group were found to have a significantly better clinical effect, in comparison to those with *E. coli*. *Bifidobacteria vs* control group: odds ratio7.32 (1.37–39.13), *E. coli vs* control group: odds ratio 0.66 (0.43–1.02). The form of UC seemingly does not impact the outcomes: mild-to-moderate UC: odds ratio 3.39 (0.97–11.87), active UC: odds ratio 3.79 (0.37–39.01), nonactive UC: odds ratio 1.26 (0.64–2.46)."

5.9 Comparison of Probiotics with Anti-Inflammatory Drugs and Placebo

Among studies that compare the impact of probiotics with that of the placebo Zigra et al. stated that the "tests that collate the impact of probiotics with that of the placebo (*Bifidobacteria vs* placebo, symbiotic *vs* placebo) gave better results than studies that compared the effect of probiotics with the effect of anti-inflammatory drugs. Among five randomized, controlled studies comparing probiotics with anti-inflammatory drugs, one of the trials showed a trend for increased efficacy. The other four studies did not find any significant difference between probiotics and anti-inflammatory agents. The pooled relative risk was 0.95 (95% CI 0.58–1.55, $p = 0.84$), showing no significant difference between probiotics and treatment with anti-inflammatory drugs. A nonsignificant heterogeneity was found ($Q = 9.63$) as the normal heterogeneity for 5 df according to the $\times 2$ distribution was 9236. Among four randomized, controlled studies with probiotics with placebo, two trials reported significantly higher remission in UC for patients receiving probiotics. The other two trials showed a trend for augmented efficacy of probiotic in comparison with placebo. The pooled relative risk was 7.32 (95% CI 1.37–39.13, $p = 0.020$), showing a significant difference between probiotic and placebo."

Table 5.2 collates several clinical trials that demonstrate the effectiveness of probiotics in IBD and IBS.

Table 5.2 Clinical trials suggesting the effectiveness of probiotics in IBD and IBS

Author	Title	Study	Results
Kajander et al. (2008)	"Clinical trial: Multispecies probiotic supplementation alleviates the symptoms of irritable bowel syndrome and stabilizes intestinal microbiota"	"The effects of multispecies probiotic supplementation (*Lactobacillus rhamnosus* GG, *L. rhamnosus* Lc705, *Propionibacterium freudenreichii* ssp. *shermanii* JS and *Bifidobacterium animalis* ssp. *lactis* Bb12) were investigated on abdominal symptoms, quality of life, intestinal microbiota and inflammatory markers in irritable bowel syndrome"	"This multispecies probiotic seemed to be an effective and safe option to alleviate symptoms of irritable bowel syndrome and to stabilize the intestinal microbiota"
Enck et al. (2009)	"Randomized controlled treatment trial of irritable bowel syndrome with a Probiotic *E. coli* preparation (DSM17252) compared to placebo"	"Two hundred and ninety-eight patients with lower abdominal symptoms diagnosed as IBS were treated for 8 weeks by the compound Symbioflor®-2 (Symbiopharm GmbH, Herborn, Germany), an Escherichia coli product ($N = 148$), or placebo ($n = 150$) in a double-blinded, randomized fashion"	"Treatment of IBS with the probiotic Symbioflor-2 was effective and superior to placebo in reducing typical symptoms of IBS patients seen by general practitioners and by gastroenterologists"
Zocco et al. (2006)	"Efficacy of *Lactobacillus* GG in maintaining remission of ulcerative colitis"	"The efficacy of *Lactobacillus* GG alone or in combination with mesalazine vs. mesalazine was evaluated as maintenance treatment in ulcerative colitis"	"*Lactobacillus* GG seemed to be effective and safe for maintaining remission in patients with ulcerative colitis, and it could represent a good therapeutic option for preventing relapse in this group of patients"
Kruis et al. (2004)	"Maintaining remission of ulcerative colitis with the probiotic *Escherichia coli* Nissle 1917 is as effective as with standard mesalazine"	"Comparison of the efficacy in maintaining remission of the probiotic preparation *Escherichia coli* Nissle 1917 and established therapy with mesalazine in patients with ulcerative colitis"	"The probiotic drug *E coli* Nissle 1917 showed efficacy and safety in maintaining remission equivalent to the gold standard mesalazine in patients with ulcerative colitis"
Rembacken et al. (1999)	"Non-pathogenic *Escherichia* coli versus mesalazine for the treatment of ulcerative	"Aim was to find out whether the administration of a non-pathogenic strain of *E coli* (Nssle 1917) was	"Results suggest that treatment with a non-pathogenic *E coli* has an equivalent effect

(continued)

Table 5.2 (continued)

Author	Title	Study	Results
	colitis: a randomized trial"	as effective as mesalazine in preventing relapse of ulcerative colitis. It was also examined whether the addition of *E coli* to standard medical therapy increased the chance of remission of active ulcerative colitis"	to mesalazine in maintaining remission of ulcerative colitis"
Guslandi et al. (2000)	"*Saccharomyces boulardii* in maintenance treatment of Crohn's disease"	"Patients with Crohn's disease in clinical remission were randomly treated for six months with either mesalamine 1 g three times a day or mesalamine 1 g two times a day plus a preparation of *Saccharomyces boulardii* 1 g daily. Clinical relapses as assessed by CDAI values were observed in 37.5% of patients receiving mesalamine alone and in 6.25% of patients in the group treated with mesalamine plus the probiotic agent"	"Results suggested that *Saccharomyces boulardii* may represent a useful tool in the maintenance treatment of Crohn's disease"
Nobaek et al. (2000)	"Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome"	"Patients were randomized into two groups, one receiving 400 mL per day of a rose-hip drink containing 5×10^7 cfu/ml of *Lactobacillus plantarum* (DSM 9843) and 0.009 g/mL oat flour and the other group receiving a plain rose-hip drink, comparable in color, texture, and taste. The administration lasted for 4 wk"	"The results of the study indicated that the administration of *Lb. plantarum* with known probiotic properties decreased pain and flatulence in patients with IBS"

5.10 Conclusion

Considerable substantiation data demonstrating that probiotics contribute to anti-inflammatory effects exists through established researches; however, mechanistic studies clearly bringing out the path by which they act are not clearly understood. It is important not to generalize the health effects from specific strain studies to species effects, whether positive or negative. Most commonly, probiotics are to be used as supplements particularly for patients who do not respond positively to regular treatment regime. Major advantage of these probiotics is that they are tolerated well by the body with insignificant adverse health effects described in the aforementioned studies.

References

Andresen V, Baumgart DC (2006) Role of probiotics in the treatment of irritable bowel syndrome: potential mechanisms and current clinical evidence. Int J Probiotics Prebiotics 1(1):11

Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, Fernandes GR, Tap J, Bruls T, Batto JM, Bertalan M (2011) Enterotypes of the human gut microbiome. Nature 473 (7346):174–180

Basso PJ, Câmara NOS, Sales-Campos H (2018) Microbial-based therapies in the treatment of inflammatory bowel disease–an overview of human studies. Front Pharmacol 9:1571

Bennet SM, Öhman L, Simrén M (2015) Gut microbiota as potential orchestrators of irritable bowel syndrome. Gut Liver 9(3):318

Canavan C, West J, Card T (2014) The epidemiology of irritable bowel syndrome. Clin Epidemiol 6:71

Caporaso JG, Lauber CL, Walters WA, Berg-Lyons D, Huntley J, Fierer N, Owens SM, Betley J, Fraser L, Bauer M, Gormley N (2012) Ultra-high-throughput microbial community analysis on the Illumina HiSeq and MiSeq platforms. ISME J 6(8):1621–1624

Celiberto LS, Bedani R, Rossi EA, Cavallini DCU (2017) Probiotics: the scientific evidence in the context of inflammatory bowel disease. Crit Rev Food Sci Nutr 57(9):1759–1768

Chermesh I, Eliakim R (2006) Probiotics and the gastrointestinal tract: where are we in 2005? World J Gastroenterol: WJG 12(6):853

Day RL, Harper AJ, Woods RM, Davies OG, Heaney LM (2019) Probiotics: current landscape and future horizons. Fut Sci OA 5(4):FSO391

Dignass A, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, D'Haens G, D'Hoore A, Mantzaris G, Novacek G, Öresland T (2012) Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohn's Colitis 6 (10):991–1030

Enck P, Zimmermann K, Menke G, Klosterhalfen S (2009) Randomized controlled treatment trial of irritable bowel syndrome with a probiotic E.-coli preparation (DSM17252) compared to placebo. Zeitschriftfür Gastroenterologie 47(02):209–214

Guarner F, Khan AG, Garisch J, Eliakim R, Gangl A, Thomson A, Krabshuis J, Lemair T, Kaufmann P, De Paula JA, Fedorak R (2012) World gastroenterology organisation global guidelines: probiotics and prebiotics October (2011). J Clin Gastroenterol 46(6):468–481

Guslandi M, Mezzi G, Sorghi M, Testoni PA (2000) Saccharomyces boulardii in maintenance treatment of Crohn's disease. Dig Dis Sci 45(7):1462–1464

Kajander K, Myllyluoma E, Rajilić-Stojanović M, Kyrönpalo S, Rasmussen M, Järvenpää S, Korpela R (2008) Clinical trial: multispecies probiotic supplementation alleviates the symptoms of irritable bowel syndrome and stabilizes intestinal microbiota. Aliment Pharmacol Ther 27 (1):48–57

Kruis W, Frič P, Pokrotnieks J, Lukáš M, Fixa B, Kaščák M, Wolff C (2004) Maintaining remission of ulcerative colitis with the probiotic Escherichia coli Nissle 1917 is as effective as with standard mesalazine. Gut 53(11):1617–1623

Li F, Duan K, Wang C, McClain C, Feng W (2016) Probiotics and alcoholic liver disease: treatment and potential mechanisms. Gastroenterol Res Pract 2016:5491465. https://doi.org/10.1155/2016/5491465. Epub 2015 Dec 29

Mack DR (2011) Probiotics in inflammatory bowel diseases and associated conditions. Nutrients 3 (2):245–264
Mahdi BM (2018) Introductory Chapter: inflammatory bowel disease. In: New concepts in inflammatory bowel disease. IntechOpen
Marteau P, Seksik P, Jian R (2002) Probiotics and intestinal health effects: a clinical perspective. Br J Nutr 88(S1):s51–s57
Ng SC, Hart AL, Kamm MA, Stagg AJ, Knight SC (2008) Mechanisms of action of probiotics: recent advances. Inflamm Bowel Dis 15(2):300–310
Nobaek S, Johansson ML, Molin G, Ahrné S, Jeppsson B (2000) Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. Am J Gastroenterol 95(5):1231–1238
Oelschlaeger TA (2010) Mechanisms of probiotic actions–a review. Int J Med Microbiol 300 (1):57–62
Pagnini C, Delle Fave G, Bamias G (2013) Probiotics in inflammatory bowel disease: pathophysiological background and clinical applications. World J Immunol 3(3):31–43
Panghal A, Janghu S, Virkar K, Gat Y, Kumar V, Chhikara N (2018) Potential non-dairy probiotic products–a healthy approach. Food Biosci 21:80–89
Rembacken BJ, Snelling AM, Hawkey PM, Chalmers DM, Axon ATR (1999) Non-pathogenic Escherichia coli versus mesalazine for the treatment of ulcerative colitis: a randomised trial. Lancet 354(9179):635–639
Spiller R, Major G (2016) IBS and IBD—separate entities or on a spectrum? Nat Rev Gastroenterol Hepatol 13(10):613–621
Vasudha S, Mishra HN (2013) Non dairy probiotic beverages. Int Food Res J 20(1)
Veerappan GR, Betteridge J, Young PE (2012) Probiotics for the treatment of inflammatory bowel disease. Curr Gastroenterol Rep 14(4):324–333
Whelan K, Quigley EM (2013) Probiotics in the management of irritable bowel syndrome and inflammatory bowel disease. Curr Opin Gastroenterol 29(2):184–189
Zhu B, Wang X, Li L (2010) Human gut microbiome: the second genome of human body. Protein Cell 1(8):718–725
Zigra PI, Maipa VE, Alamanos YP (2007) Probiotics and remission of ulcerative colitis: a systematic review. Neth J Med 65(11):411–418
Zocco MA, Dal Verme LZ, Cremonini F, Piscaglia AC, Nista EC, Candelli M, Armuzzi A (2006) Efficacy of lactobacillus GG in maintaining remission of ulcerative colitis. Aliment Pharmacol Ther 23(11):1567–1574