

## Review

# Role of Probiotics and Their Metabolites in Inflammatory Bowel Diseases (IBDs)

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**Abstract:** Inflammatory Bowel Disease (IBD) is a term used to describe a group of complex disorders of the gastrointestinal (GI) tract. IBDs include two main forms: Crohn's Disease (CD) and Ulcerative Colitis (UC), which share similar clinical symptoms but differ in the anatomical distribution of the inflammatory lesions. The etiology of IBDs is undetermined. Several hypotheses suggest that Crohn's Disease and Ulcerative Colitis result from an abnormal immune response against endogenous flora and luminal antigens in genetically susceptible individuals. While there is no cure for IBDs, most common treatments (medication and surgery) aim to reduce inflammation and help patients to achieve remission. There is growing evidence and focus on the prophylactic and therapeutic potential of probiotics in IBDs. Probiotics are live microorganisms that regulate the mucosal immune system, the gut microbiota and the production of active metabolites such as Short-Chain Fatty Acids (SCFAs). This review will focus on the role of intestinal dysbiosis in the immunopathogenesis of IBDs and understanding the health-promoting effects of probiotics and their metabolites.

**Keywords:** Inflammatory Bowel Diseases (IBDs); gut microbiota; dysbiosis; probiotics; metabolites; Short-Chain Fatty acids (SCFAs); alternative therapeutic approaches



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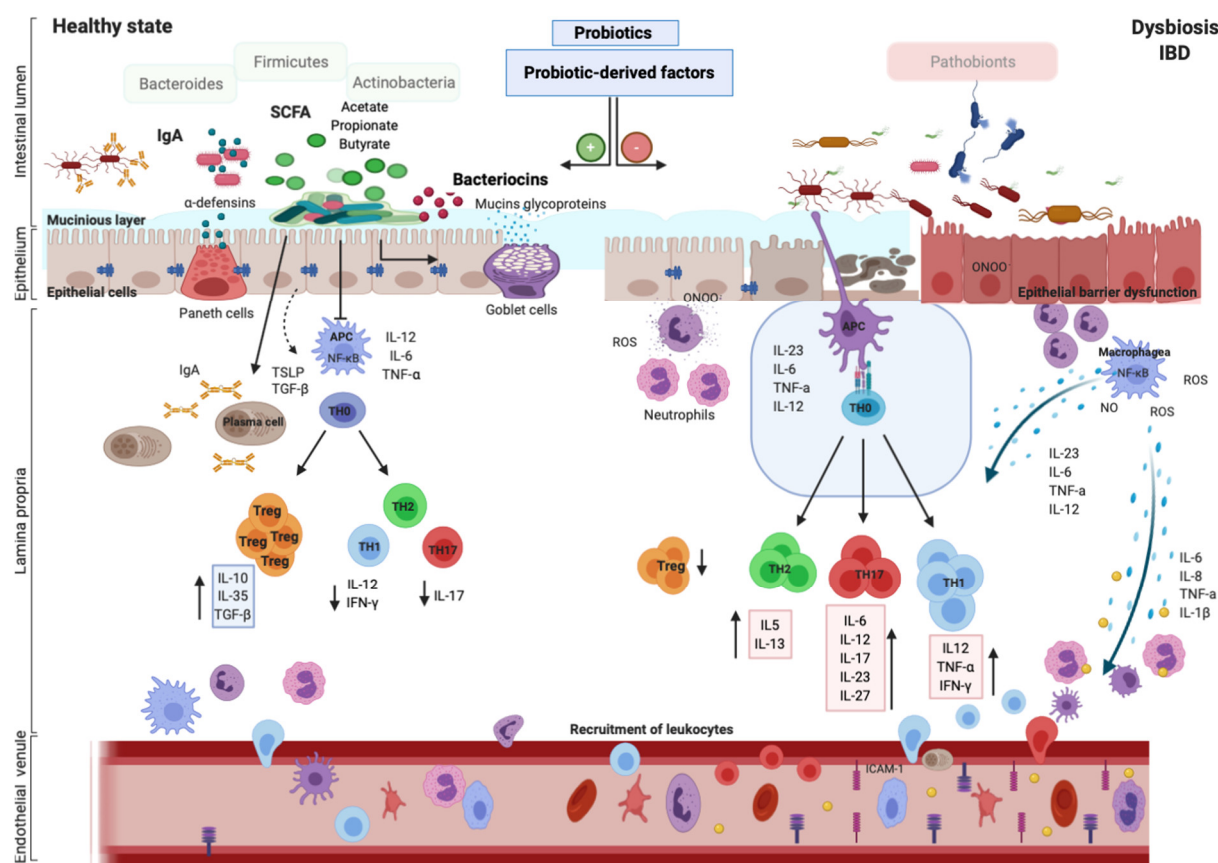
## 1. Introduction

Crohn's disease (CD) and Ulcerative colitis (UC) are the main forms of Inflammatory Bowel Diseases (IBDs). They are chronic disabling conditions that affect the gastrointestinal (GI) tract and cause several clinical symptoms, including diarrhea, rectal bleeding and abdominal pain [1,2]. Crohn's Disease and Ulcerative Colitis commonly appear in early adulthood [3]. However, the younger population is also affected, with more cases in pediatric and in adolescent patients in the last two decades [4]. The incidence of IBD varies considerably in the world. Indeed, CD and UC were initially described as pathologies affecting mainly the industrialized countries. Currently, their incidence is increasing worldwide probably due to a greater urbanization and improvement in hygiene [4,5].

The intestinal inflammation in CD is transmural involving "skip areas" of any segment of the gastrointestinal tract. Whereas in UC, the inflammation is continuous and affects mainly the colon [1–3]. The exact factors that trigger the chronic and relapsing intestinal inflammation remain unknown. However, it is now widely accepted that IBDs result from a deregulated and ongoing immune response towards intestinal microbial antigens in genetically predisposed individuals under several environmental factors [6,7].

The disturbance of the immune response in IBDs is classically characterized by the predominance of a TH1 type immune response in CD promoted by the transcription factors Signal Transducer and Activator of Transcription 4 (STAT-4) and T-box expressed in T cells (T-bet) and marked by high secretion of Interferon-gamma (IFN- $\gamma$ ), Interleukin-12 (IL-12) and Tumor Necrosis Factor-Alpha (TNF- $\alpha$ ). UC is characterized by an atypical TH2 type immune response promoted by the expression of the transcription factors STAT-6 and GATA binding protein 3 (Gata-3), which generates high levels of IL-5, IL-13 and IL-4 [8,9].

Moreover, abnormal activation of TH17 and deregulation of the balance between the different subsets of effector cells and T regulatory cells (Treg) characterize both conditions [10–12]. Decreased number and function of Treg cells leads to insufficient regulation of the immune response during the active phase of the disease (Figure 1) [13]. Consequently, the intestinal mucosa in IBDs is infiltrated by inflammatory cells that release cytokines, chemotactic molecules, Reactive Oxygen Species (ROS) and Nitric Oxide (NO). These pro-inflammatory mediators trigger and perpetuate a chronic inflammatory response in the gut, leading to tissue damage and disease [12,14].



**Figure 1.** Immunopathogenic mechanisms in Inflammatory Bowel Diseases (IBDs) and potential beneficial role of probiotics. Commensal bacteria are essential for the development and the proper functioning of the mucosal immune system and the protection of the epithelial barrier integrity. Probiotics and their derived factors (metabolites) participate in intestinal homeostasis through several direct and indirect mechanisms. IBDs are characterized by an altered epithelial barrier and the infiltration of the intestinal mucosa by inflammatory cells that release cytokines, chemotactic molecules, reactive oxygen species and nitric oxide. APC: Antigen presenting Cell; SCFAs: Short-Chain Fatty Acids; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells. Th: T helper; TNF-α: tumor necrosis factor alpha; IL: interleukin, NO: Nitric oxide; ROS: Reactive oxygen species, ICAM-1: Intercellular Adhesion Molecule 1 IFN-γ: Interferon gamma, Treg: Regulatory T cells; (OONO-): Peroxynitrite.

In the intestine, the mucosal immune system is continually exposed to a dynamic and complex microbial ecosystem called gut microbiota. To maintain the intestinal homeostasis in the host, a crosstalk between the immune system and over 1000 different species of microorganism has been established. In IBDs, the dialogue between the microbiota and the immune system is interrupted. An alteration of the gut microbiota function and diversity (referred to as dysbiosis) and a dysregulation of the mucosal immune response are observed. They constitute the cornerstones of the physiopathology (Figure 1) [15,16].

Both CD and UC are relapsing and remitting conditions alternating flare of active inflammation followed by periods of remission. The main goals of therapy in IBDs are in-

ducing and maintaining the clinical remission while improving the quality of life of patients by lowering the risk of complications and reducing the need for surgery. The conventional therapies (Salazosulfamide, Glucocorticoids and Immunosuppressive agents) are often accompanied by side effects or lose their effectiveness over time in some patients [3,17]. Therefore, highlighting a new alternative and complementary therapeutic approach that targets both the deregulated immune response and the dysbiosis characterizing IBDs is of great interest.

In the last decade, probiotics have emerged as an interesting therapeutic approach for IBDs. Probiotics are living microorganisms belonging to the gut microbiota. They promote beneficial health effects when ingested in adequate amounts [18]. Several clinical trials and experimental studies reported the beneficial effects of probiotics in a variety of GI disorders. Their exact mechanism of action is still not well understood, but probiotics seem to be able to improve the intestinal microbial balance, maintain the integrity of the intestinal epithelial barrier and modulate local and systemic immune responses [19]. Probiotics can act by direct contact with the immune and Intestinal Epithelial Cells (IECs) or through the secretion of active metabolites such as butyrate, a short-chain fatty acid that exerts numerous anti-inflammatory and cytoprotective actions [20]. The use of such metabolites has been proposed to overcome the risk of infection associated with the ingestion of large bacterial loads.

This review will focus on describing the involvement of the dysbiosis in the onset of IBDs and understanding the potential beneficial effects of probiotics and their metabolites as a complementary and alternative therapeutic approach.

## 2. Functional Role of the Gut Microbiota

Microbial colonization of the gastrointestinal tract begins in the newborn as soon as the fetal membrane breaks. After two to three years of life, the intestinal flora reaches its equilibrium to become a personal fingerprint. The gut microbiota represents all the microbial species, including bacteria, fungi, archaea and viruses permanently present in the gastrointestinal tract of the host. It is made up of  $10^{14}$  microorganisms that are essentially strict anaerobic bacteria [20]. Three dominant phylogenetic groups characterize the intestinal microbiota of the healthy adult: Firmicutes, Bacteroidetes and Actinobacteria; within these phyla, six bacterial genera are found in all individuals: Eubacterium, Lactobacillus, Enterococcus, Clostridium, Bacteroides and Bifidobacterium [21,22]. The gut microbiota exerts several metabolic, trophic and protective functions essential to the host physiology. By metabolizing undigestible derived polysaccharide substrates, commensal bacteria produce SCFAs: acetate, propionate and butyrate (Figure 1). The latter represents 70% of the energetic sources of colonocytes [23]. Butyrate not only regulates the proliferation, differentiation and apoptosis of epithelial cells but also help to maintain the balance between TH17 cells and Treg cells in the colon [24]. Furthermore, commensal bacteria are involved in the transformation of xenobiotics and the production of vitamins (B12, B6, B9 and K). They strengthen the intestinal epithelial barrier through several mechanisms such as: defense against pathogens by competition for nutrients, production of antibacterial factors, induction of IgA secretion and mucus production goblet cells (Figure 1) [25]. The impact of the gut microbiota on host physiology extends beyond the gut and seems to exert profound effects on mood, motivation and higher cognitive functions. Currently, numerous studies focus on highlighting the interplay between the microbiota and the gut-brain axis [26].

The recognition of commensal microorganisms by the immune cells and IECs relies mainly on a family of receptors known as Pattern Recognition Receptors (PRRs), which recognize structures common to groups of commensal and pathogenic microorganisms that have remained constant during evolution, the PAMPS (Pathogen Associated Molecular Pattern). The main PRRs expressed by the IECs are Toll-Like Receptors (TLRs) and Nucleotide-Binding Oligomerization Domain (NODs). Their activation triggers different signaling pathways that lead to the activation of innate immune response and contribute to

the development of the adaptive immune response [27]. Commensal bacteria are, therefore, essential for the development and the proper functioning of the mucosal immune system. Experimental studies using germ-free (axenic) mice revealed numerous abnormalities of the mucosal immune system: a reduced number of Peyer's patches, a decreased number of IgA secreting plasma cells and Treg cells [28]. Interestingly, it has been shown that colonization of the gastrointestinal tract by commensal bacteria or the oral administration of TLRs ligands to axenic mice leads to the restoration of their mucosal immune system [29]. Bouskra et al. have shown that recognition of peptidoglycan from Gram-negative commensal bacteria by the NOD1 receptor is sufficient to induce the genesis of Isolated Lymphoid Follicles (ILFs) [30].

Furthermore, the microbiota plays a determining role in the polarization of lymphocytes (TH1, TH2) and the maintenance of the balance between the TH17 and Treg cells [16,24]. Indeed, it has been shown that commensal microorganisms exert an anti-inflammatory function by interfering with the activation of the Nuclear Factor-kappa B (NF- $\kappa$ B) signaling and the production of pro-inflammatory cytokines [31,32]. In addition, they promote the differentiation of tolerogenic Dendritic Cells (DCs) by inducing the production of Thymic Stromal Lymphopoietin (TSLP) and Transforming Growth Factor-beta (TGF- $\beta$ ) by IECs [33]. Given the essential role of the gut microbiota in the intestinal homeostasis and host physiology, it is possible to suggest that the intestinal dysbiosis is a key factor in the development of IBDs.

### 3. Alteration of Gut Microbiota in IBDs

Among the first evidence incriminating the gut microbiota in the development of IBDs is the effective responses to antibiotic treatments in some patients and by finding microbial agents or their components in inflammatory lesions that usually occur in the segments of intestine with the highest concentration of microorganisms (e.g., colon and ileum) [34,35]. These observations were consolidated by data from experimental studies using germ-free mice which resist to colitis in absence of the endogenous flora [16,36,37]. Furthermore, Genome-Wide Association Studies (GWAS) revealed that most of IBDs associated-susceptible genes are implicated in sensing microbes and activation of the immune response [38–40].

Advances in next-generation sequencing technology have significantly contributed to current understanding of the involvement of gut microbiota in intestinal inflammation. The microbial imbalance in IBDs is characterized by a reduced biodiversity and richness of the commensal flora and an increase in the number of certain pathogenic microorganisms (pathobionts) (Figure 1) [41–43]. The most prominent change in the gut microbiota composition was observed in Crohn's disease. It is marked by a significant and specific reduction of *Faecalibacterium prausnitzii* that belongs to the firmicute phyla on one hand, and by the predominance of members of the Proteobacteria phyla on the other hand. *Faecalibacterium prausnitzii* is one of the most abundant human gut bacteria and appears to be a marker of gut health due to its anti-inflammatory and immunoregulatory properties. One of its well-demonstrated functions is the production of anti-inflammatory metabolites such as butyrate [21,38,44–46]. Currently, the factors that cause the reduced abundance of *Faecalibacterium prausnitzii* in CD are still unclear. Moreover, the contradictory results obtained by Hansen et al. in a pediatric cohort of CD showing a high level of *Faecalibacterium prausnitzii* emphasize the complex role of the gut microbiota in the onset of the intestinal inflammation [47].

The involvement of specific pathobiont candidates in IBDs is largely investigated. The most incriminated are *Mycobacterium avium*, enteropathogenic strain of the B2 phylotype *E. coli* (Adherent-invasive *Escherichia coli*) and *Campylobacter concisus* [48]. Several studies using humanized gnotobiotic (hGB) mouse model are shedding light on the causal involvement of specific microbial communities in the onset of inflammation [16]. However, it should not be ignored that intestinal dysbiosis does not only concern bacterial communities



but also extends to yeasts. The study of Sokol et al. identified a fungal microbiota dysbiosis in IBDs along with the bacterial dysbiosis [49].

#### 4. Role of Probiotics and Their Active Metabolites in IBDs

The history of probiotics began over a century ago when Metchnikoff attributed the longevity of certain Bulgarian and Armenian populations to their regular consumption of fermented milk rich in Lactic Acid Bacteria (LAB) [50]. The term probiotic comes from the Greek language “pro bios” meaning “for life,” which is opposed to that of antibiotic meaning “against life.” In 2001, the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) defined Probiotics as “live microorganisms, which when administered in adequate amounts, may confer a health benefit” [18]. Among the microorganisms defined as probiotic, there are LAB, bifidobacteria, the Gram-negative bacterium *Escherichia coli* Nissle 1917 and the non-pathogenic yeast *Saccharomyces boulardii* [19].

Evidence of the effectiveness of probiotics has been reported in several gastrointestinal diseases (e.g., irritable bowel syndrome, traveler’s diarrhea, UC and pouchitis) and allergic diseases (e.g., atopic dermatitis) [51,52]. The administration of the non-pathogenic strain *E. coli* Nissle 1917 showed equivalent efficacy and safety to mesalazine (5-aminosalicylic acid) used in induction and maintenance therapy in adult patients [53] and in children with UC [54]. The orally administered probiotic cocktail VSL#3 containing: *Lactobacillus plantarum*, *Lactobacillus delbrueckii* subsp. *Bulgaricus*, *Lactobacillus paracasei*, *Lactobacillus acidophilus*, *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis* and *Streptococcus* subsp. *thermophilus* has been shown to be effective in inducing remission in patients with mild to moderate UC and not responding to conventional therapy [55] and in reducing inflammation in pouchitis [56,57]. Moreover, the non-pathogenic yeast *Saccharomyces boulardii* has been shown to be effective in preventing relapse from active disease in patients with Crohn’s disease [58,59]. *Saccharomyces boulardii* has been shown to be effective in preventing recurrent *Clostridium difficile* infections (CDIs) caused by *Clostridium difficile*, an anaerobic gram-positive spore forming and toxin producing bacilli. In IBDs, especially UC, a high susceptibility to CDIs has been reported due to different factors, such as antibiotic therapy that alters the microbiota and increases the risk of *Clostridium difficile* infection.

Prophylactic and therapeutic effects of probiotics have been demonstrated in several animal models of colitis. The exact mechanisms underlying the beneficial effects of probiotics are still poorly defined. However, it has been shown that it depends on the strain, dose and the severity of the colitis. The administration of VSL#3 has been shown to be effective in attenuating ileitis in SAMP1/YitFc mice [60] and TNBS induced colitis in mice [61]. However, it failed to heal Dextran Sulfate Sodium (DSS)-induced chronic colitis in mice [62].

Probiotics participate in intestinal homeostasis through their direct and indirect effects on the modulation of gut microbiota and the immune system. It has been demonstrated that certain probiotics are able to down regulate the expression of pro-inflammatory cytokines by interfering directly with the activation of NF- $\kappa$ B pathway [31,63–65] or via the activation of the nuclear receptor Peroxisome Proliferator-Activated Receptor-Gamma (PPAR- $\gamma$ ) [66,67]. In our previous studies, we have shown the beneficial effects of the probiotic mixture Ultrabiotique® containing (*Lactobacillus acidophilus*, *Bifidobacterium lactis*, *Lactobacillus plantarum* and *Bifidobacterium breve*) in a DSS-induced experimental model of colitis. The colonic mucosa of treated mice showed a decreased expression of TLR-4, NF- $\kappa$ B and Inducible Nitric Oxide Synthase (iNOS) [68,69].

Furthermore, numerous in vivo and in vitro studies have highlighted the ability of probiotics such as VSL#3 to induce the differentiation of tolerogenic DCs through down regulation of the expression of CD40 and CD80 co-stimulatory molecules, the production of IL-12 and the induction of IL-10 production [70–72]. Tolerogenic DCs promote the differentiation of Forkhead Box P3 (Foxp3+) Treg cells capable of exerting immunosuppressive activities by secreting IL-10 and TGF- $\beta$  [73]. Similarly, an in vitro study reported

the ability of *Lactobacillus delbrueckii* and *Lactobacillus rhamnosus* to induce the generation of tolerogenic DCs from monocytes isolated from Systemic Lupus Erythematosus (SLE) patients [74]. The anti-inflammatory effects of VSL#3 seem also to be mediated through the interaction of unmethylated bacterial CpG DNA motifs with the intracellular TLR-9 receptor present in plasmacytoid Dendritic Cells (pDCs), which lead to the production of Type I Interferon [75].

In addition to the modulation of the immune system, probiotics may compete with pathogens for nutrients and attachment sites on the surface of the epithelium. They are also capable of producing antimicrobial molecules or inducing the production of  $\beta$ -defensins by Paneth cells (Figure 1) [19,76,77]. They can reduce the severity of colitis by modulating the composition of the gut microbiota and by strengthening the barrier functions of the intestinal epithelium. Indeed, both in vivo and in vitro studies showed the ability of probiotics to increase *Muc* gene expression and enhance the secretion of mucus by goblet cells and undifferentiated colonic HT29 cell lines, respectively [68,78]. Mucus layer covering the epithelium plays an essential role in protecting the host against bacterial invasion and in maintaining the integrity of the intestinal epithelium. Furthermore, probiotics can decrease epithelial permeability by enhancing tight junction stability and up regulation of the expression of tight junction proteins (e.g., occluding, Zonula occludens (ZO)-1) [79,80].

Currently, growing evidence supports the importance of microbial metabolism for the intestinal homeostasis and recommend the use of probiotic supernatants as therapeutic strategy in IBDs. The culture supernatant of probiotic constitutes the culture medium in which the microorganisms were grown and then removed by filtration. Thus, it is devoid of any micro-organism and presents no risk of infection. The culture supernatant of probiotics contains a mixture of extremely diverse metabolites such as SCFAs, proteins, phospholipids and bacteriocins [25]. In IBDs, the concentration of butyrate is significantly lower compared to healthy controls reflecting metabolic alterations likely caused by the dysbiosis [81,82]. Butyrate is mainly produced by bacteria of the clostridial clusters IV (*Faecalibacterium prausnitzii*) and XIVa (*Eubacterium rectale*) belonging to the firmicutes phylum [83]. It has been shown that the culture supernatant of *Faecalibacterium prausnitzii* contains butyrate, which exerts in vivo and in vitro anti-inflammatory functions. Indeed, butyrate down regulates the production of pro-inflammatory mediators such as TNF- $\alpha$  and IL-8 through the inhibition of NF- $\kappa$ B [49,63,84–86]. Butyrate plays a critical role in the maintenance of the effectors T Cells/Treg balance by promoting Treg response. Moreover, it may act as an epigenetic regulator through inhibition of Histone Deacetylase (HDACs), which leads to the inactivation of NF- $\kappa$ B, the down regulation of pro-inflammatory cytokines production and the amplification of the suppressive function of FOXP3+ Treg cells [87–89]. Recently, it has been shown that *Faecalibacterium prausnitzii* produces an anti-inflammatory protein called “MAM” able to inhibit NF- $\kappa$ B activation [90]. Other probiotic strains such as *Lactobacillus acidophilus* and *Lactobacillus rhamnosus* GG have been shown to release extracellular proteins that are able to reduce the pro-inflammatory response and inhibit cytokine-induced apoptosis in intestinal epithelial cells [91].

The production of Butyrate and other SCFAs by the gut microflora can be stimulated by nondigestible food ingredients such as oligosaccharides. The most common prebiotics are Fructo-Oligosaccharides FOS (inulin and oligofructose). They stimulate the growth and activity of Lactobacilli and Bifidobacteria. The synergistic combination of probiotics with prebiotics is called ‘Synbiotics’ [92].

Although clinical studies in IBD patients are encouraging, probiotic usage as a “bio-therapy” is still a matter of debate as research in this innovative field is a relatively new frontier of investigation. In fact, a large number of clinical studies did not achieve their goals. They showed potential limitations due to a high heterogeneity observed in enrolled patients (e.g., active and inactive stage of IBD, disease localization) the relatively short duration of the studies and the association with other treatments such as 5-ASA mesalazine and/or immunosuppressants. Moreover, other parameters are related to the bioavailability

of the probiotics, the efficacy of individual probiotics strains, route of administration and doses.

## 5. Conclusions

It is still unclear whether the intestinal dysbiosis is a cause or a consequence of the chronic inflammation in IBDs. Pro-, pre- and synbiotics appear to be a promising approach that targets both the deregulated immune response and the intestinal dysbiosis. Overall, experimental studies and clinical trials have shown encouraging results in IBDs. In UC, probiotics help maintaining longer remission and improving the quality of life of patients. They have been shown to be as effective as the gold standard treatment mesalazine. Unlike with UC, fewer studies were able to support the beneficial effects of probiotics in active CD. Although CD and UC share similar clinical symptoms, they differ by the anatomical localization of lesions and the cellular and molecular mechanisms of pathology. These key differences between UC and CD seems to impact the efficacy of probiotics therapy and the responsiveness of patient to treatment. Even if pro-, pre- and synbiotics appear to be relatively well tolerated by patients, their exact mechanism of action is not fully established. More studies in well-designed and conducted Randomized Controlled Trials (RCTs) need to be focused on the determination of appropriate dosage and strain of probiotic on the different categories and stages of IBDs.

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