Chapter

Efficiency of Treatment Targeted on Gut Microbiota in Inflammatory Bowel Diseases: Current Strategies and Perspectives

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Abstract

Inflammatory bowel diseases (IBDs) represent a category of diseases characterized by intestinal inflammation and include two main entities, ulcerative colitis and Crohn's disease, one of the representative clinical characteristics of which being chronic diarrhea. The etiology of these diseases is multifactorial, combining genetic, immunological, and also environmental factors, along with gut dysbiosis. In recent years, we encountered a higher incidence of IBD cases and of severe forms of disease. Therefore, there is an urgent need to develop new and efficient treatments, including strategies to improve the microbiome. In this chapter, we will discuss the current knowledge about the impact of different therapies influencing gut microbiota, such as prebiotics, probiotics, synbiotics, and other agents in IBD prevention, and also in the induction/maintenance of IBD remission. The manuscript will focus also on potential areas for research in the future using agents that modify intestinal microbiota and combined strategies.

Keywords: chronic diarrhea, inflammatory bowel diseases, microbiota, prebiotics, probiotics, synbiotics

1. Introduction

Inflammatory bowel diseases (IBDs) represent a category of diseases characterized by intestinal inflammation and include two main entities, ulcerative colitis and Crohn's disease, one of the representative clinical characteristics of which being chronic diarrhea. The etiology of these diseases is multifactorial, combining genetic, immunological, and also environmental factors, along with gut dysbiosis (**Figure 1**). In recent years, we encountered a higher incidence of IBD cases and of severe forms of disease. Therefore, there is an urgent need to develop new and efficient treatments, including strategies to improve the microbiome (**Figure 2**). In this chapter, we discuss

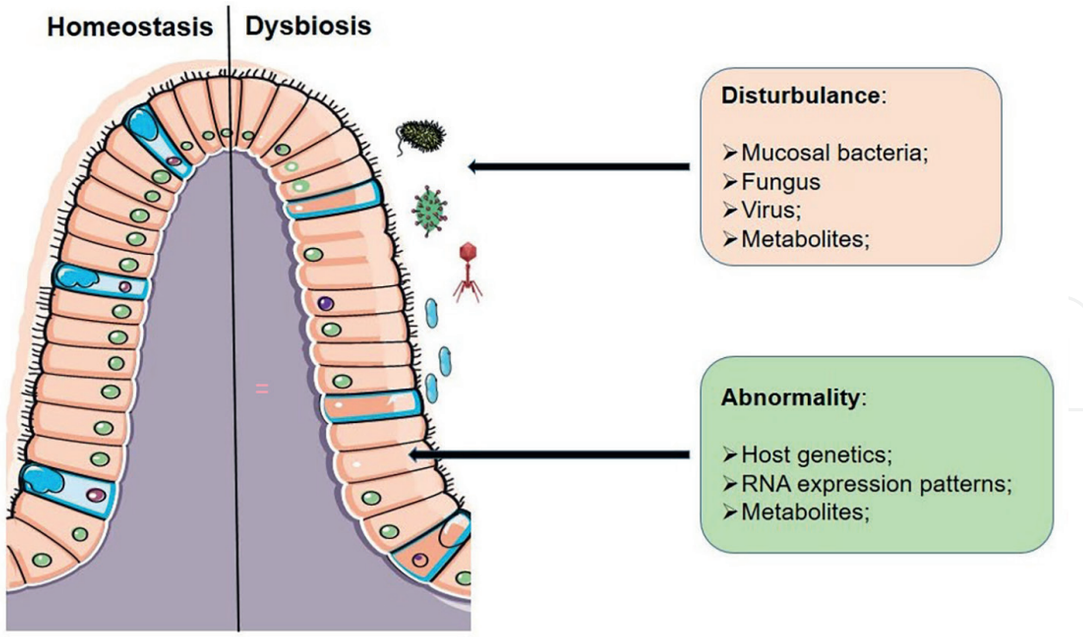

Figure 1.
The intestinal micro-environment dysbiosis in multi-dimension.

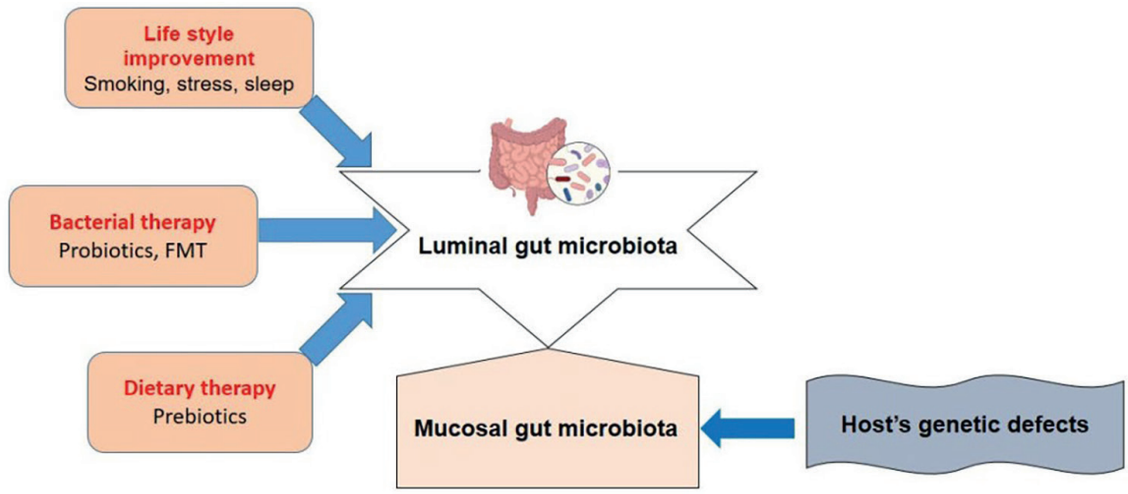

Figure 2.
Factors influencing microbiota.

the current knowledge about the impact of different therapies influencing gut microbiota, such as prebiotics, probiotics, synbiotics, and other agents in IBD prevention, and also in the induction/maintenance of IBD remission. The manuscript focuses also on potential areas for research in the future using agents that modify intestinal microbiota and combined strategies.

2. Gut microbiota modulation therapies

These therapies include different types of medical approaches; the chapter includes the most recent and relevant clinical data regarding the main strategies of treatment.

2.1 Nutritional therapies

2.1.1 Exclusive enteral nutrition (EEN)

This nutritional therapy has been recommended as first-line, steroid-sparing treatment for pediatric CD since the 1990s and provides the entire calorie and nutrient requirements using liquid formulations delivered either orally or through nasogastric tube or gastrostomy, for a period of 6–8 weeks. It is associated with remission rates of 60–80%, and the efficacy is not correlated with the formula types or the route of administration [1–6]. Most studies investigating the mechanism of action of EEN focused on the changes in gut flora and microbial metabolites as a potential mechanism, showing conflicting data. The first study on microbiota changes related to EEN used 16S ribosomal DNA polymerase chain reaction and temperature gradient gel electrophoresis and discovered important modification of the band profile associated with different bacterial species [7]. Later studies showed that although children treated with EEN had higher rates of mucosal healing, they still have a lower proportion of butyrate-producing bacteria in comparison with steroid-treated patients. A recent research revealed differences in the fecal metabolome of responders vs. non-responders to EEN [8, 9]. There are few data on the impact of EEN on the microbiota of adult CD patients; one study that investigated microbiota changes in adult CD patients treated with EEN for 2 weeks prior to intestinal resection for strictures found a significant decrease in alpha diversity and in the Enterobacteriaceae family, but which did not modify the postoperative recurrence [10].

2.2 Prebiotics and dietary fiber

Prebiotics are defined by the International Scientific Association for Probiotics and Prebiotics (ISAPP) as a "substrate that is selectively utilized by host microorganisms conferring a health benefit" [11, 12].

The most commonly used fibers in patients with digestive diseases are non-digestible soluble fibers that are fermented by the bacteria from the colon, leading to an increase in the concentration of some healthful bacterial metabolites such as short-chain fatty acids (SCFA). Soluble fiber, such as inulin, fructooligo- (FOS) and galactooligo-saccharides (GOS), lactulose and derivatives of galactose and β-glucans, proved to be efficient for the gut health, by both modulating gut microbiota and by exerting anti-inflammatory properties. These fibers can be naturally found in a huge number of products of plant origin and also added in different food products for nutritional and health purposes [6]. They increase the volume of the intestinal contents (by binding to water) and maintain the correct pH. Prebiotics increase the number of beneficial bacteria from the gut microbiome (i.e., the Lactobacillus, Bifidobacterium, and Bacteriodes families) and inhibit the pathogens [13, 14]. Also, they have a beneficial influence on the metabolism of lipids (lowers serum cholesterol level), glucose, and proteins, and increase the absorption of calcium, iron, and magnesium [11].

In order to be categorized as a prebiotic, a product must meet several conditions [12]:

- It should stimulate the proliferation and activity of some beneficial strains of gut bacteria

- It should create a favorable medium to some beneficial bacteria in the colon

- It should decrease the pH in the intestinal lumen
- It should be resistant to the action of digestive enzymes and process of hydrolysis
- It should not be absorbable in the upper digestive tract
- It should not be destroyed during the food processing process

2.2.1 Clinical studies on prebiotics in IBD

Research data demonstrate that prebiotics determine the change of gut microbiota spectrum and bacteria metabolites, but there are still few data published regarding prebiotics in IBD.

Benjamin et al. [15] performed a randomized, double-blind, placebo-controlled study, assessing the effect of FOS administration on active CD. The study was performed on 54 patients with CD and 49 controls; patients with active CD were randomized to receive FOS or placebo for a period of 4 weeks. Data showed a clinical worsening of the CD patients receiving prebiotics.

The results of another study showed that oral lactulose had no beneficial effect in active IBD (clinical, endoscopic, or histopathological activity), but it improves significantly the QoL in UC patients [16]. The multicenter clinical trial of Kanauchi et al. using germinated barley foodstuff (GBF) treatment in patients with mild-to-moderate active UC for 24 weeks showed significant improvement of clinical activity [17]. A research assessing the administration of inulin enriched with FOS in the same type of patients for 2 weeks demonstrated a significant reduction in the value of stool calprotectin [18].

Another study assessed the effect of GFB treatment for 12 months in inactive UC patients, revealing a lower rate of relapse [19]. A randomized, placebo-controlled study investigated the efficiency of ispaghula husk supplementation for 4 months in patients presenting inactive UC. They found a significantly higher rate of clinical improvement in the intervention group vs. placebo (69% vs. 24%) [20]. The study of Fernandez-Benarez investigated the effect of Plantago ovata seeds on three different groups of inactive UC (105 patients)—treated with mesalamine alone, Plantago ovata seeds with mesalamine, and Plantago ovata seeds alone for a period of 12 months, finding similar remission rates for all groups, but significant increase in stool butyrate levels in the groups treated with Plantago ovate [21].

To date, results of prebiotic research in patients with IBD are conflicting. Although the administration of prebiotic agents may be associated with some adverse digestive side effects in active IBD, their administration in early childhood for a proper development of gut microbiome and later prevention of IBD onset should be taken into consideration.

2.3 Probiotics

The human intestine is colonized by 10–100 trillion commensal bacteria that are involved in the digestion process, modulation of immune response, and other functions. Nowadays, due to excessive use of antibiotics, stress conditions, and hygiene, we encounter gut dysbiosis. Lactic-acid-producing bacteria (LAB) include the biggest part of the microbiome, which produce lactic acid as a result to the anaerobic digestion of saccharides. Lactobacillus spp. are the most important group of bacteria found

in fermented food (e.g., pickles, soured milk, kefir) and are considered to be beneficial for humans [22, 23].

Probiotics are live organisms that are beneficial for the gut by modulating the immune response—increase the IgA production and enhance the host immune system`s defenses—and are able to compete with pathogens [24, 25]. Their favorable actions on human gut are the following [26–29]:

- The production of components with antibacterial activity (e.g., lactic acid, bacteriocins, hydroperoxides)
- Competitively block the binding sites on the epithelial cells and upregulate tight junction molecules of the mucosal barrier
- The degradation of the receptors for toxins
- Change of intestinal pH
- Competition for essential nutrients

The beneficial effect of probiotics was known through antibiotic-based therapy [30, 31] to decrease blood cholesterol level [32], the treatment of local infections [33], and others. In case of IBD patients, there is an abnormal activation of the immune system due to chronic intestinal inflammation. Prebiotics modulate the immune system in the mucosa layer of the intestine, by stimulating the production of antibodies, promoting phagocytosis and NK activity, determining T cell apoptosis, enhancing anti-inflammatory cytokines while reducing the pro-inflammatory ones.

2.3.1 Clinical studies and meta-analysis with probiotics in IBD

The randomized double-blind study by Tamaki et al. [24] performed in patients with mild/moderate UC demonstrated a reduction in clinical activity assessed by Ulcerative Colitis Activity Score (UCDAI), though not reaching statistical significance, in 28 patients treated with Bifidobacterium longum 536 vs. 28 patients in the placebo group, after 8 weeks of follow-up. They observed a statistically significant improvement in rectal bleeding and endoscopic activity assessed by Mayo scale.

A single-center, randomized, double-blind and placebo-controlled study [34] in patients with UC in clinical remission compared a group of patients treated with Bio-Three (Streptococcus faecalis T-110, Clostridium butyricum TO-A, and Bacillus mesentericus TO-A), with a placebo group for a period of 1 year, demonstrated lower relapsing rate in the study group, but statistically significance was reached only at 3 months of study. Yilmaz et al. [35] performed a prospective open-label randomized control, single-center study that assessed the administration of fermented milk (400 ml of kefir daily) for 4 weeks. Their results showed a statistically significant reduction of the inflammatory syndrome, improvement of hemoglobin level, and results of good feeling score, in both CD and UC patients from the study group in comparison with controls. The randomized, placebo-controlled trial of Shadnoush et al. [36] on IBD patients remarked significantly higher amounts of Lactobacillus, Bifidobacterium, and Bacteroides in patients treated with yogurt vs. control group after 8 weeks.

A study compared effect of the treatment with mesalazine and a probiotic blend (Lactobacillus salivarius, Lactobacillus acidophilus, and Bifidobacterium bifidus BGN4) vs. mesalazine alone for 24 month in patients with moderate-to-severe UC demonstrated a statistically significant improvement in endoscopic activity and clinical symptoms in the first group vs. the group with aminosalicylates treatment, suggesting that the combined treatment could be a feasible alternative to steroid treatment [37]. Another study [38] compared a group treated with mesalazine and Bifico (containing Enterococcus faecalis, Bifidobacterium longum, and Lactobacillus acidophilus) vs. a group treated with mesalazine alone. After 40 days of treatment, a significant reduction in Enterobacteria, Enterococci, Saccharomyces, and Bacteroides and increases in Bifidobacteria and Lactobacilli, and also lower levels of CRP, fecal lactoferrin, alpha-1-antitrypsin and beta-2-microglobulin, IL-6, and higher level of IL-4 in the study group were noticed. The study of Su et al. [39] randomized patients with CD to two study groups, one treated with probiotics (Bifidobacterium and Lactobacillus) combined with sulfasalazine and prednisone and the other one treated with sulfasalazine alone, which were further compared with a healthy control group. Authors noticed a significant reduction in the pro-inflammatory cytokines, better therapeutic efficiency, and lower infection rate in the study group.

Bjarnason et al. [40] randomized 81 patients with UC and 61 with CD into two groups, one using multistrain probiotic agent named Symprove that contains Lactobacillus rhamnosus NCIMB 30174, Lactobacillus plantarum NCIMB 30173, Lactobacillus acidophilus NCIMB 30175, and Enterococcus faecium NCIMB 30176 with a second group of placebo. They noticed a statistically significant improvement in the level of fecal calprotectin in patients with UC treated with multistrain probiotic agent, without significant differences in other parameters. The multi-center, randomized, placebo-controlled study of Fedorak et al. (2015) [41] on 120 patients with CD who underwent ileocolonic surgical resection compared the study group treated with VLS#3 (an agent that contains viable bacteria, including four strains of Lactobacillus combined with three strains of Bifidobacterium and one strain of Streptococcus salivarius subspecies thermophilus) vs. a placebo group. After 1 year of follow-up, there were found lower rates of severe endoscopic recurrence and significant reductions in pro-inflammatory cytokine levels in the study group treated with VLS#3 vs. control group.

One study evaluated the effect of administration of the Bifidobacterium breve strain Yakult (BFM) found in fermented milk in patients with UC vs. placebo regarding the relapse-free survival and incidence of relapse, but they found no significant differences [42].

Asto et al. [43] performed a meta-analysis in which they evaluated 18 placebo-controlled studies (1997–2018), including 1491 patients with UC who were treated with prebiotics, probiotics, or synbiotics vs. placebo groups; although any significant effect in maintaining remission was not demonstrated, it could be concluded that probiotics are beneficial in achieving remission in the active phase of UC. The results of the meta-analysis of Zhang et al. [44] comprising 38 studies demonstrated that probiotics, prebiotics, and synbiotics are efficient in achieving and maintaining remission, and their use determined a reduction in UC disease activity index. Probiotics lead to an increase in the number of intestinal Bifidobacteria, and synbiotics were more efficient in comparison with probiotics and prebiotics.

The meta-analysis of Jia et al. [45] included 10 studies (1999–2013), most of them focusing on *E. coli* Nissle and VSL#3. The results demonstrated significant differences between *E. coli* Nissle vs. mesalazine in the remission rate, risk of recurrence, and

occurrence of complications; also, statistically significant higher rates of remission and lower risk of recurrence were obtained with VLS#3 vs. control groups. Puvvada et al. [46] analyzed three RCTs, which examined the effect of probiotics on the QoL of patients with IBD (two of them with positive results). The authors concluded that probiotics have beneficial effects of the QoL of IBD patients.

2.3.2 Side effects of probiotics

The meta-analysis of Dore et al. [47] on the incidence of side effects related to the use of probiotics in IBD patients that included nine trials (826 patients) demonstrated a higher percentage of side effects in the group of patients treated with probiotics; this effect was remarked only in patients with UC, but not with CD. These studies referred to more digestive side effects, abdominal pain occurring significantly more often in patients using probiotics. Later (2020), the same group performed a retrospective cohort study on IBD patients, 100 taking probiotics (VSL#3, Lactobacillus reuteri, and a mixture of S. thermophiles and L. acidophilus, B. breve and B. animalis ssp. Lactis) and 100 controls, showing that the incidence of adverse effects (need for systemic steroids, hospitalization, and surgery) was lower in patients taking probiotics (more than 75% of the duration of IBD) and especially in UC patients [48].

Probiotics are commonly considered as safe agents, reducing the adverse effects of the IBD, but we have to keep in mind that exceptionally, in immunosuppressed patients, bacterial translocation and sepsis may develop.

2.3.3 Probiotic engineering in the treatment of IBD

The use of probiotics helps the transition from a pro-inflammatory to an anti-inflammatory state at the gut level. Nowadays, the strains currently available as probiotics are represented by the Bifidobacterium species, Enterococcus faecium, Lactobacillus strains, Saccharomyces boulardii, Bacillus species, and Pediococcus, which have been demonstrated to be associated with the beneficial health effects [27, 49, 50]. Probiotic engineering determines the formation of bacterial strains with more powerful properties to target the enteric pathogens and to specifically intervene in IBD. These types of probiotics have the capacity to synthesize in situ a one or multitude of desired therapeutic biomolecules able to act on gut inflammation and avoid the side effects and complications associated with current treatment. This strategy uses bacteria or yeasts genetically engineered with the genes for some therapeutic agents that are acting as anti-inflammatory agents [22, 51].

One of the strategies used in probiotic engineering used a xylan-inducible system in Bacteriodes ovatus, which was able to induce some important biomolecules for the maintaining of gut integrity [52].

Many cytokines have been involved in IBD. Lactococcus lactis has been engineered to produce anti-inflammatory cytokine IL-10 [53]. IL-10 treatment proved to be promising in animal models of IBD and also in clinical trials using IBD patients [49]. Results of two trials performed by IBD Cooperative Study Group demonstrated an improvement of the disease in 23.5% of patients receiving IL-10 vs. placebo [54–58]. IL-27 is known to play a crucial role in infectious diseases, autoimmunity, and cancer in many organs and systems, including the digestive tract. In an animal model, treatment with IL-27 was able to diminish experimental colitis. Moreover, in colitis mouse models, engineered IL-27-producing L. lactis demonstrated to be more efficient than both the IL-10-producing L. lactis and systemic administration of IL-27 [59–61].

Interleukin 35 (IL-35) is an anti-inflammatory cytokine from the IL-12 family and plays an important role in immune suppression. IL-35 plays a pivotal role in the development and the function of both regulatory B (Bregs) and T cells (Tregs). IL-35 functions as a new anti-inflammatory factor for IBD and other immune diseases. Therapeutic potential of recombinant IL-35 protein was assessed in DSS-induced colitis mouse model. Recombinant IL-35 protein could slow down the pathologic process in mouse model. Trefoil factors (TFF) and anti TNF-α nanobodies (single domain antibody fragments) represent other therapeutic agents that have been constitutively expressed in L. lactis and tested in DSS-induced colitis in mice [49]. The former have protective and reparative properties on the intestinal epithelium. The peptides produced *in situ* by L. lactis were considerably more effective at healing colitis than the oral or rectal administration of the purified TFF [49].

One recent study engineered E. coli Nissle 1917 to produce an extracellular matrix including all three trefoil factors in order control inflammation. Tumor necrosis factor (TNF) is a pro-inflammatory cytokine secreted in IBD, and antibodies for this cytokine are used nowadays as a treatment for IBD, but associated with some side effects and disadvantages. Oral administration of nanobody-secreting L. lactis leads in local delivery of anti-mTNF nanobodies in the gut and was associated with a significant reduction of inflammation in a mouse model of DSS-induced colitis. This way of administration has been proved to prevent the systemic side effects of anti-TNF through localized delivery [62].

2.3.4 Probiotic engineering in vaccinations

Traditional oral vaccinations may fail to resist in the harsh gastric environment and, sometimes, they are unable to act on the most important immune structures that induce immunity. Furthermore, there is the possibility of reversion to a virulent state of the attenuated microbes [63]. On the other hand, engineered probiotics have the following advantages:

- are able to deliver medication/vaccinations where these types of vaccinations are effective in inducing intestinal immunity
- are more easier to store and are much cheaper than the conventional biologics [64]
- have increased survival potential under unfavorable environmental conditions
- can be manipulated to determine a tolerogenic immune response
- can be specifically targeted to some immune structures such as Peyer's patches [65].

But we have to take into considerations several disadvantages related to safety concerns. Bioengineered probiotics represent microbes and are genetically modified organisms (GMO) [66]; therefore, they pose some challenge for the approval of administration. Moreover, patients may be skeptic about their safety and their effects on the environment. To prevent bacterial gene transfer and survival in the natural medium, specific guidelines and containment strategies as well as specific engineering methods can be developed.

2.4 Synbiotics

Synbiotics represents a combination of prebiotics and probiotics with synergistic beneficial effect, but for now there are still few literature data on their effect on IBD patients; more often, they contain Lactobacillus GG and/or Bifidobacteria combined with FOS and/or inulin [67, 68]. In the double-blind trial of Steed et al. [69], patients with active CD were randomized to receive 6 g per day of either a synbiotic (a combination of inulin and FOS) vs. placebo for 6 months. The results demonstrated significant reduction in the clinical and histopathological activity of CD, an increased population of Bifidobacteria species in the study group, and a decrease in TNF alpha after 3 months (but not 6 months). Another randomized, double-blind and placebo-controlled study [70] evaluated the same symbiotic for a period of 1 month, revealing significant improvement in the endoscopic and histopathological activity in the rectal biopsies and reduction in serum CRP, TNF-α, and IL-1 α and mucosal human beta defensins 2, 3, 4.

The randomized, double-blind and placebo-controlled trial of Chermesh et al. [71] investigated Synbiotic 2000 including four probiotics and four prebiotics administrated for 24 months found no significant differences between the study group and placebo regarding clinical picture, laboratory data, and endoscopic activity. Fujimori et al. [72] included 120 patients with UC (active and inactive) that were randomized into three groups, first treated with probiotic (Bifidobacterium longum), the second with prebiotic (Psyllium), and the third one with symbiotic (bifidobacterium longum plus psyllium) for 4 weeks, observing a significant improvement in the QoL and decrease in CRP level in the group treated with symbiotic vs. the other two groups. Another study investigated 41 patients with mild-to-moderate UC, randomized into two groups, one with standard treatment associated with symbiotic (Bifidobacterium breve strain Yakult plus GOS) vs. the second group treated only with standard treatment. After 1 year of treatment, authors noticed significant reduction in clinical and endoscopic activity in study group vs. control [73].

2.5 Paraprobiotics

Paraprobiotics are represented by dead probiotic bacteria cells and cell constituents. The idea of treating with inactivated bacterial strains or fragments or even bacterial metabolite products instead of probiotics is reasonable taking into consideration the risk of administrating probiotics in sepsis, immunosuppressed subjects, and premature babies [74, 75]. They are manufactured by cultivating selected strains of bacteria and their subsequent inactivation [76, 77].

The advantages of paraprobiotic administration are the following [78–80]:

- the absence of risk of bacterial translocation
- the absence of risk of transferring antibiotic resistance genes
- are easier to produce, transport, and store
- more precise therapeutic effects due to their administration in adequate amounts
- possibility to be used even in preterm neonates` treatment
- multidirectional way of action, the most important being immunomodulation

Several highly efficient bacterial strains for the health have been selected to be used as paraprobiotics: Bifidobacterium lactis Bb12, Bifidobacterium longum, Lactobacillus gasseri OLL2716, Lactobacillus brevis SBC8803, and Lactobacillus delbrueckii subsp. bulgaricus OLL1073R-1 and Saccharomyces cerevisiae. Moreover, proteins and peptides, polysaccharides (glucans), and fragments of genetic material in the form of AT DNA obtained from Lactobacillus spp. have similar effects [81].

At the moment, there are several *in vitro* studies demonstrating the beneficial immunomodulatory effect of paraprobiotics in IBD patients. Also, some of the paraprobiotic proteins can improve the regeneration of the intestinal mucosa, and yeast cell wall components may improve digestion.

In vitro studies demonstrated immunomodulatory, anti-inflammatory, antiproliferative, and antioxidant effects of paraproteins, which seem to be able to prevent and improve the clinical symptoms of IBD patients [82–84].

2.6 Postbiotics

The term postbiotics refers to metabolites and cell-free supernatants (CFS) and also soluble factors such as metabolic bioproducts secreted by live microbes [80]. Metabiotics refers to the structural constituents of probiotic bacteria and/or their metabolites and/or specific signaling molecules that can improve physiological functions of the body and regulatory or metabolic reactions related with gut microbiota [85, 86].

Postbiotics are found in fermented food (kefir, sauerkraut, yogurt, certain pickles, etc.) and inside the human body. They are mainly represented by organic acids (i.e., short-chain fatty acids (SCFA)), tryptophan (Trp), and bacteriocins and present direct benefits due to their action on the host cells and indirect benefits related to the stimulation of proliferation of beneficial gut bacterial strains and inhibition of harmful microbial strains. They may have different properties depending on their type; the most important benefit is related to their anti-inflammatory and antioxidant effects.

2.6.1 SCFAs

They are produced by the intestinal fermentation of dietary fiber, non-starch polysaccharides (NSP), and resistant starch, mainly in the proximal part of the large bowel, in relationship with the substrates and the microbiota. The most important SCFAs are represented by acetic acid (AA), propionic acid (PA), and butyric acid (BA), and a proper SCFA ratio helps the immune system. Also, they have the capacity to acidify the environment, which is considered by some researchers to be beneficial by improving the bioavailability of metals and by protecting against the pathogenic bacteria, but harmful by others due to the supposed damage of the intestinal mucosal barrier [87–90].

2.6.1.1 Butyric acid (BA)

BA represents one of the most potent SCFAs, acting both in intestinal and parenteral way [91].

The complex intestinal effects of BA are the following [92–95]:

- represents one of the primary energy sources for colonocytes
- has a protective intestinal effect by enhancing the expression of mucin genes and mucin production

- stimulates the proliferation of normal enterocytes and inhibits the proliferation of cancerous cells ("butyrate paradox") secondary to the inhibition of histone deacetylase (HDAC)

- decreases the expression of genes involved in the synthesis of the major pro-inflammatory cytokines by inhibiting the activity of the NF-κB complex in the immune cells

- presents an antioxidant effect by increasing the level of reduced glutathione

At the moment, there are inconclusive results of the clinical studies using either rectal infusions or oral formulas with BA in patients with IBD.

The parenteral effect of BA, produced also though the inhibition of HDAC, consists of [96–98]:

- stimulates hemoglobin synthesis and increases the number of reticulocytes, therefore leading to amelioration of anemia in IBD patients

- determines the secretion of anti-inflammatory cytokine IL-10 and aldehyde dehydrogenase by binding to a specific receptor expressed in adipocites and immune cells

- enhances the detoxification process and the removal of electrophilic compounds in association to the stimulation of Treg lymphocyte differentiation

2.6.1.2 Propionic acid (PA)

PA is found naturally in dairy products secondary to the natural fermentation by Propionibacterium and also may be added as food preservative. PA produced in the intestine by the fermentation process of different compounds determined by anaerobic flora comprises a much higher proportion compared with the amount delivered with food [99]. The effects of PA reside in [11, 100]:

- antibacterial and antifungal effects—it inhibits the genes of pathogenic bacteria and prevents gut colonization with pathogens from Sallmonela family

- inhibition of local inflammation by diminishing COX2 enzymes and formation of prostaglandins

- anti-inflammatory properties:

  - inhibits lymphocyte proliferation

  - activates the synthesis of anti-inflammatory resistin in adipose tissue

  - inhibits TNF-α release by neutrophils and endothelial cells

  - represents the most potent ligand of GPCR43, a receptor exposed to immunocites, proving a strong relationship with the immune system

2.6.1.3 Acetic acid (AA)

There are discordant results concerning AA, some research suggesting stimulation of the proliferation of neoplastic tissue, others inhibition of the neoplastic tissue during hypoxia, and even onset of metabolic syndrome and obesity [101, 102].

2.6.1.4 Adjuvant treatment with SCFA in IBD

Vernia et al.(1995) [103] used enemas twice daily for a period of 6 weeks vs. placebo group; they obtained statistically significant decreases in intestinal bleeding and urgency, as well as an improved patient self-evaluation score compared with placebo. The study of Lührs et al. [104] compared the efficiency of a butyrate enema versus a placebo, used twice daily for a period of 8 weeks. They showed that study patients presented a significant reduction in the number of macrophages with NF-kB expression and also a decreased number of neutrophils in crypt and epithelia and of lymphocytes and plasma cells of the lamina propria, proved in bioptic specimens, in correlation with the disease activity. Another study performed a randomized, prospective evaluation of corticosteroid enemas and mesalazine enemas vs. SCFA enemas in patients with distal UC (proctosigmoiditis), proving similar recovery rates between these three groups [105].

The study of Hamer et al. [93] using rectal enemas with sodium butyrate vs. saline for 20 days in patients presenting distal UC in clinical remission demonstrated minor effects induced by butyrate on colonic inflammation and oxidative stress. They proved the effect of BA on colonic glutathione levels. Another randomized trial [106] investigated sodium butyrate enemas for 2 weeks vs. placebo in patients with distal UC non-responsive to conventional treatment. The authors found a significant decrease in the number of stools, blood discharge, endoscopic score of severity, and histologic score of inflammation in patients treated with SCFA enemas. Scheppach et al. [107] compared enemas of combined SCFA, butyrate, or saline placebo in patients with active distal UC twice daily for 8 weeks showing a trend toward a beneficial effect of SCFA enemas. Some other studies were not able to prove the efficiency of treatment with SCFA enemas [108, 109]. They were able to show that only patients with colitis dating back less than 6 months responded significantly more to SCFA vs. placebo. In conclusion, the results of most studies using SFCA are inconsistent.

2.6.2 Tryptophan (Trp)

Tryptophan represents a fine regulator of inflammation involved in the adaptive immunity, mucosal barrier, and intestinal homeostasis. Gut microbiota metabolizes tryptophan, through this influencing serotonin and the immune system. Most products of the bacterial metabolism of tryptophan represent ligands for the aryl hydrocarbon receptor (AhR) that mediate the expression of genes responsible for the metabolism of xenobiotics (i.e., dioxins, drugs) metabolized by the cytochrome P450. Tryptophan metabolites such as AhR ligands are essential in the gut mucosal protection against inflammation and for maintaining intestinal homeostasis by helping mucosal barrier integrity and acting on many immune cell types. The metabolism of Trp generates some bioactive postbiotic derivatives, including indole acetate and propionate indole. Host enzymes involved in Trp metabolism (IDO1 enzyme) have a positive effect on clinical activity of IBD [110–114].

In patients with IBD, it was suggested that pro-inflammatory cytokines initiate the conversion of Trp to its metabolites. A very small amount of ingested Trp is conversed to serotonin, which acts not only on the CNS but also on the digestive tract, influencing gut vasodilation, motility, secretion, and absorption processes. Trp and its metabolites represent potential therapeutic targets in IBD. In this regard, trials using the administration of Lactobacillus, which produces AhR agonists, were able to demonstrate a decrease of colonic inflammation in animal models [115, 116].

2.7 Antibiotics

Antibiotics may have an insecure effect on the gut microbiota homeostasis, leading to an increase in Enterobacteriaceae and reduction in Clostridia, representing a possible pre-IBD state [117]. Moreover, IBD patients treated with antibiotics have an increased risk of developing an overgrowth of pathogenic microbes (e.g., Clostridioides difficile), fungi (e.g., candida), and bacteriophages [118]. Antibiotics have been widely used, in both pediatric and adult IBD especially in situations (pouchitis, perianal disease, abdominal abscesses), but even in luminal disease. Suggested potential mechanisms for the role of antibiotics in IBD patients include [119, 120]:

- direct influence on the gut microbiota, stimulating anti-inflammatory flora (e.g., Bacteroides and Firmicutes), while reducing bacteria that are associated with inflammation (Enterobacteriaceae—Escherichia coli, Fusobacterium)

- change metabolic enzymatic pathways determined by gut bacteria

- target pathobionts that are invading the mucosa in CD

In most of the cases, antibiotics are used empirically, without identification of a specific microbial target. A case series [121] with very early-onset IBD patients refractory to other conventional treatments, mean age of 1.6 years, demonstrated that oral administration of Vancomycin ± Gentamycin can induce sustained remission.

The Cochrane systematic review of Townsend et al. [122] assessed the efficacy and safety of antibiotic administration for induction/maintenance of remission in CD. There were 13 RCTs included, comprising 1303 patients. Comparisons included ciprofloxacin/rifaximin/metronidazole/clarithromycin/cotrimoxazole vs. placebo, ciprofloxacin plus metronidazole vs. methylprednisolone, ciprofloxacin, metronidazole and budesonide vs. placebo with budesonide, ciprofloxacin vs. mesalazine, ciprofloxacin plus adalimumab vs. placebo with adalimumab, ciprofloxacin plus infliximab vs. placebo with infliximab, clarithromycin and antimycobacterial vs. placebo, and metronidazole plus cotrimoxazole vs. placebo. All antibiotics were pooled as a class vs. placebo, and antibiotics plus anti-TNF vs. placebo with anti-TNF. There was an uncertain effect of individual antibiotics on CD patients due to imprecision. Considering antibiotics as a class, 55% of the patients treated with antibiotic failed to achieve remission at 6–10 weeks vs. 64% of placebo group; 41% of the patients with antibiotic failed to achieve a clinical response at 10–14 weeks vs. 49% of placebo group (RR 0.77). The effect of antibiotics on relapse and on serious AE was unclear. They do not seem to increase the risk of AEs. The most frequent adverse events included gastrointestinal distress, upper respiratory tract infection, abscess development, headache, change in taste, and paresthesia. When antibiotics were combined with anti-TNF, 21% of patients on associated therapy failed to achieve a clinical response/remission

at week 12 vs. 36% of placebo patients (RR 0.57, low certainty evidence); 77% of the combined group had an AE compared with 83% with placebo (RR 0.93). In active CD, evidence suggests a modest benefit provided by antibiotics that may not be clinically significant. In this context, more research is needed to establish the efficacy and safety of antibiotic treatment for maintenance of remission in CD patients.

In the future, due the development of microbiome evaluation techniques, by assessing the specific gut microbiome from patient stool samples before treatment, we will be able to select the right IBD candidates for antimicrobial treatment [123] in order to target specific pathobionts or to favorable modulate microbiome/metabolome.

2.8 Fecal microbiota transplantation (FMT) for the treatment of IBD

The study of Zhang et al. [124] investigating the role of FMT in an UC mouse model induced by dextran sulfate sodium demonstrated that FMT intervention decreased disease activity index levels and the histopathological changes, reduced the expression of colonic cytokines and oxidative stress, restored the gut microbiota, and increased the concentrations of gut SCFAs.

The systematic review of Imdad et al. (2018) [125] included four studies (277 participants), which assessed the efficiency of FMT for the treatment of UC, most of the subjects presenting mild-moderate forms of disease; authors did not find any eligible trials for the treatment of CD. Three of the studies administered FMT *via* the rectal route and one study *via* the nasoduodenal route. Combined data suggest that FMT increases the percentage of clinical remission by twofold in patients with UC compared with control group, 37% (52/140) of FMT patients vs. 18% (24/137) of control subjects achieving remission (RR 2.03). One of the studies reported that none of the patients receiving FMT relapsed at 12 weeks vs. 20% of control (RR 0.28). It was inconclusive whether there is a difference in serious adverse event (SAE) rates between the FMT and control groups, including worsening of the disease needing intravenous steroids/surgery, infections (e.g., Clostridium difficille, cytomegalovirus), small bowel perforation, and pneumonia. Common adverse events included digestive symptoms, upper respiratory tract infection, fever, headache, and dizziness. At 8 weeks, 49% (68/140) of FMT patients vs. 28% (38/137) of controls achieved clinical response (RR 1.70). Also, 30% (35/117) of FMT vs. 10% (11/112) of control subjects (RR 2.96) achieved endoscopic remission.

The systematic review and meta-analysis of Fang et al. [126] investigated the efficacy and safety and protocol of FMT for IBD, including a total of 596 pediatric and adult patients, out of which 459 received FMT. Data showed that patients with moderate-severe attacks of disease could develop significantly higher remission rates with FMT vs. patients with mild-moderate attacks. Also, in case of UC patients, FMT determined significantly higher clinical remission rates vs. placebo (28% vs. 9%, P=0.0003). The authors conclude that FMT represents an efficient and safe therapy for IBD patients (both pediatric and adult). In this meta-analysis, the type of donor stool (fresh/frozen), route of delivery, and antibiotic pretreatment proved to have no impact in patients with IBD. Due to these results, they considered FMT as a potential rescue therapy, possibly even an initial therapy for IBD.

Sokol et al. [127] performed a randomized, single-blind and sham-controlled pilot study of FMT in adults with colonic/ileocolonic CD who were enrolled while receiving oral corticosteroid in active disease. After achieving clinical remission, patients were randomized to receive either FMT or sham transplantation, while receiving a

second colonoscopy at week 6. The primary endpoint consisted of the implantation of the donor microbiota at week 6 (Sorensen index > 0.6). In this study, eight patients received FMT and nine patients sham transplantation. Data revealed that none of the patients included reached the primary endpoint. Because a low similarity index between donor and recipient gut microbiota in several patients was detected, authors assume that a single FMT might not be sufficient to induce significant changes. However, FMT demonstrated to be more efficient over sham transplantation in decreasing Crohn's Disease Endoscopic Index of Severity (CDEIS) and CRP level, and a higher colonization by donor microbiota leads to the maintenance of remission. These results must be confirmed in larger studies.

At this time, we can conclude that, although there were some clinical benefits seen in UC patients treated with FMT, there is still some uncertainty regarding the rate of serious adverse events related to FMT treatment in IBD patients. Moreover, further studies are needed to evaluate the efficacy of FMT treatment for induction of remission in CD patients (**Figure 3**). Future research should define the optimal parameters of FMT (delivery route, frequency, volume, type of preparation, type of donor, and also the type of IBD and severity of the attack). Also, more data regarding long-term maintenance of remission with FMT treatment in IBD patients are needed, along with validation regarding long-term safety of FMT.

2.9 Phage therapy

Research studies assessed the association of the enteric virome and IBD, showing alterations of the virome patients with IBD. One study showed an increased

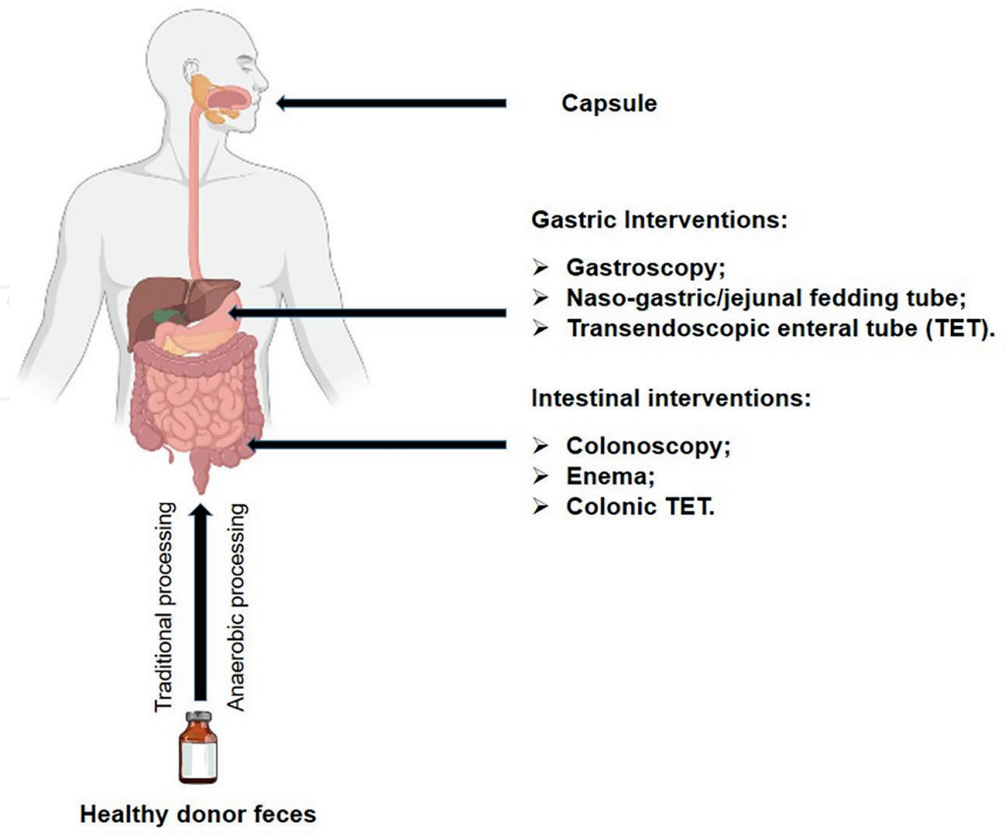

Figure 3.
Fecal microbiota transplantation regimen.

number of phages infecting some bacteria such as Clostridiales, Alteromonadales, and Clostridium acetobutylicum, along with a higher number of viruses from the Retroviridae family in IBD patients [128, 129]. A follow-up study identified a significantly higher diversity from phages associated with a reduction in bacterial diversity in subjects with IBD vs. controls. In a pediatric population with IBD, Caudovirales were more significantly represented. [130]. Higher abundance and reduced diversity of phages and a decreased number of phage-related functions in patients with UC [131] were discovered; these aspects suggest the possibility of new treatments targeting the virome in this IBD subtype.

"Phage therapy" signifies the modulation of phageome, and by this, the bacteriome of an individual suffering from a disease considered to stem from bacterial origin (**Figure 4**). It includes several steps [132]:

- changing the genetic information of an existing phage for successful adsorption to a specific bacterial strain
- preparation of one/more phage strains
- development of a dosing schedule
- administration of the preparation to the patient

In this regard, phages engineered to be usable for treatment should not be recognized by the immune system of the host. Several studies revealed the ability of phages to stimulate the production of antibodies, findings that could assign phages negative effects on the gut environment. However, there are data showing that phages may also have anti-inflammatory effects. For example, the modulation of NF-κB activity by Staphylococcus aureus phage was discovered [133]. It is considered that the systemic presence of phages could play a crucial role in diminishing the immune response and the development of some auto inflammatory/inflammatory diseases including IBD.

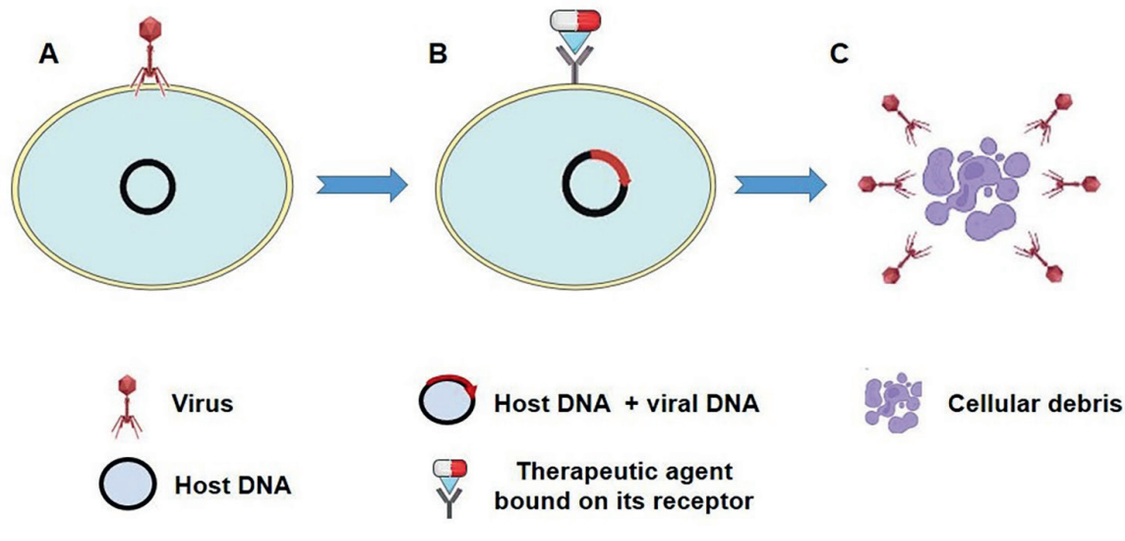

Figure 4.
Phage therapy modulation. A—the phage attachments to the host; the incorporation of the genetic information into the DNA of the host; B—the administration of the therapeutic agent; C—the degradation of the bacterium.

Górski et al. found that the phages can traverse the mucosa and enter the systemic circulation, a phenomenon discovered even in healthy subject and associated with immunomodulation [134]. Inflammation increases the intestinal permeability, and a higher number of phages enter in the circulation.

In an IBD patient, it was considered important to be able to introduce a "phage cocktail" into the colon that is not able to incorporate its genetic information into bacteria. Therefore, phages may be engineered to lack the enzyme determining the genome integration [135]. On the other hand, it may be more useful to control the switch between lytic/lysogenic life cycles, as it might be more beneficial if the phage stayed incorporated in the gut bacterial genome able to act in case of a dysbiotic state [132].

2.9.1 Fecal microbiota transplantation as a tool for phage therapy

One of the first studies focusing on the composition of the virome after FMT found the transfer of viral sequences from a healthy donor to pediatric UC patients. Among the sequences, the members of Siphoviridae were transferred with greater efficiency than other groups [136]. Of particular importance is also a study by Broecker et al., who found the phage population of a recipient CDI patient after FMT to be very similar to the donor in contrast to the composition of bacteria. [137].

The study of Ott and colleagues [138] demonstrated that the administration of sterile donor fecal matter to patients with Clostridium difficile infection, showing the cessation of symptoms. It is suggested that the effect of FMT can be at least partially

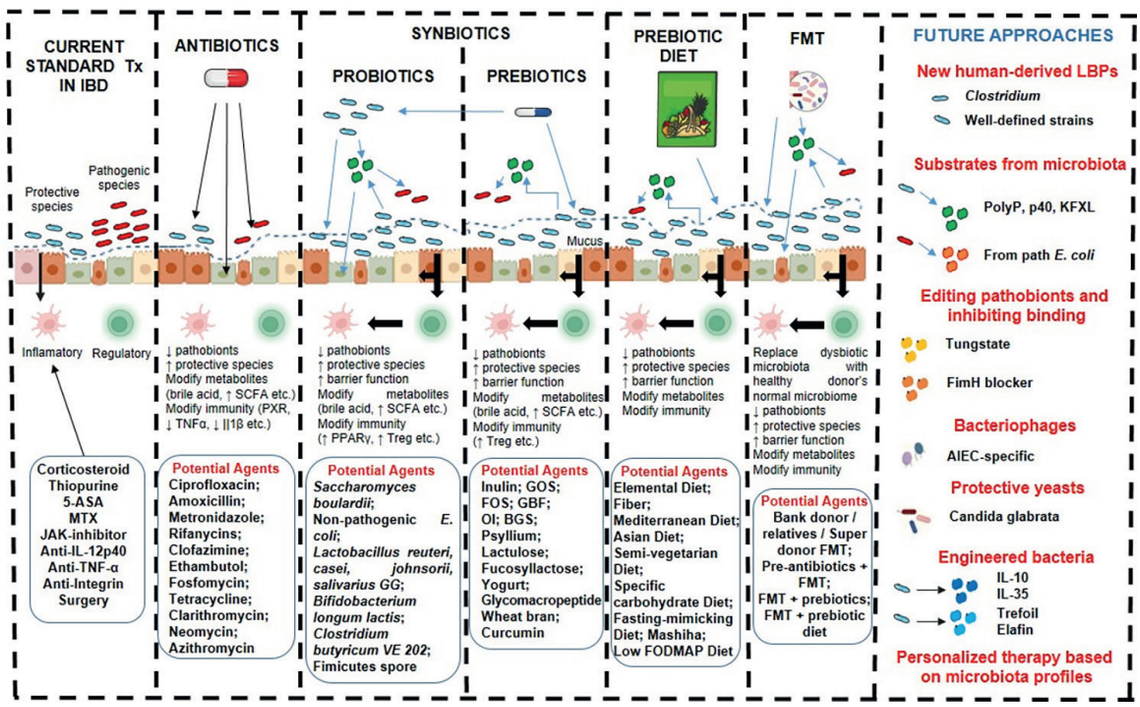

Figure 5.
Schematic overview regarding the status of current standard therapy and microbial-targeted therapies as well as future treatment approaches in IBD. Legend: Tx—therapy; 5-ASA—5-aminosalicylic acid; MTX—methotrexate; JAK—Janus kinase; IL—interleukin; TNF—tumor necrosis factor; SCFA—short chain fatty acid; PXR—pregnane X receptor; PPAR—peroxisome proliferator activated receptor; Treg—regulatory T cell; GOS—galacto-oligosaccharide; FOS—fructo-oligosaccharide; GBF—germinated barley foodstuff; OI—oligofructose-enriched inulin; BGS—bifidogenic growth stimulator; FODMAP—fermentable oligosaccharide; disaccharide, monosaccharide and polyol; FMT—fecal microbiota transplant; LBP—live biotherapeutic product; PolyP—polyphosphate; KFXL—Kangfuxin liquid; path—pathogenic; AIEC—adherent-invasive E. coli.

determined by different parts of the bacterial cell and even non-viable bacterial vectors and phages action.

2.9.2 Safety and efficiency of phage therapy

Galtier et al. [139] infected mice with an adherent-invasive E. coli strain known to be implicated in IBD pathogenesis and administered phage preparation to murine gut sections, living animals, and homogenates of ileal biopsies obtained from CD patients, obtaining a decrease in the colony-forming units of the E. coli strain and a reduction of the clinical picture of dextran sodium sulfate-induced colitis in mice.

Many research studies were not able to find any serious life-threatening adverse effects related to phage treatment [140–142]. A phase I therapy of venous leg ulcers in humans also demonstrated no safety concerns [143]. Another study using transfer of whole viral communities *via* FMT between humans shows that none of the transferred viruses infected human cells [136]. These results highlight the safety of phage therapy, without the development of any serious side effects.

An overview of the current microbial-targeted therapies as well as future treatment approaches for patients with IBD is presented in **Figure 5**.

3. Conclusions: trends toward a personalized treatment in IBD

IBD patients comprise a genetically and clinically heterogeneous population, with particular phenotypes of the disease, severity of the disease, and specific gut microbiota, aspects that lead to different activation of the immune system, response to treatment and disease evolution.

For these reasons, future efforts should be made toward initiation of a personalized treatment in IBD, based on specific evaluation of the gut microbiota and of the profile of the immune system in these patients. This attitude will allow a better understanding of the pathogenesis of IBD and the implementation of specific targeted treatments for the restoration of gut microbiome and correction of bacterial metabolic functions, along with the restoration of the regulatory immune system. In this context, we expect a safer and more efficient therapeutic approach for the management of IBD patients, using novel therapeutic arsenal.

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References

[1] Ashton J, Gavin J, Beattie RM. Exclusive enteral nutrition in Crohn's disease: Evidence and practicalities. Clinical Nutrition. 2019;**38**:80-89

[2] Hansen T, Duerksen DR. Enteral nutrition in the management of pediatric and adult Crohn's disease. Nutrients. 2018;**10**:537

[3] Wall C. Use of exclusive enteral nutrition in adults with Crohn's disease: A review. World Journal of Gastroenterology. 2013;**19**:7652-7660

[4] Levine A, Rhodes JM, Lindsay JO, Abreu MT, Kamm MA, Gibson PR, et al. Dietary guidance from the International Organization for the Study of inflammatory bowel diseases. Clinical Gastroenterology and Hepatology. 2020;**18**:1381-1392

[5] Van Rheenen PF, Aloi M, Assa A, Bronsky J, Escher JC, Fagerberg UL, et al. The medical management of paediatric Crohn's Disease: An ECCO-ESPGHAN Guideline Update. Journal of Crohn's & Colitis. 2021;**15**:171-194

[6] Eindor-Abarbanel A, Healey GR, Jacobson K. Therapeutic advances in gut microbiome modulation in patients with inflammatory bowel disease from pediatrics to adulthood. International Journal of Molecular Sciences. 2021;**22**:12506

[7] Lionetti P, Callegari ML, Ferrari S, Cavicchi MC, Pozzi E, De Martino M, et al. Enteral nutrition and microflora in pediatric Crohn's disease. Journal of Parenteral and Enteral Nutrition. 2005;**29**:S173

[8] Quince C, Ijaz UZ, Loman N, Eren AM, Saulnier D, Russell J, et al. Extensive modulation of the fecal metagenome in children with Crohn's disease during exclusive enteral nutrition. The American Journal of Gastroenterology. 2015;**110**:1718-1729

[9] Pigneur B, Lepage P, Mondot S, Schmitz J, Goulet O, Doré J, et al. Mucosal healing and bacterial composition in response to enteral nutrition vs steroid-based induction therapy—A Randomised Prospective Clinical Trial in Children with Crohn's Disease. Journal of Crohn's & Colitis. 2019;**13**:846-855

[10] Costa-Santos MP, Palmela C, Torres J, Ferreira A, Velho S, Ourô S, et al. Preoperative enteral nutrition in adults with complicated Crohn's disease: Effect on disease outcomes and gut microbiota. Nutrients. 2020;**70**:100009

[11] Martyniak A, Medynska-Przeczek A, Wedrychowicz A, Skoczen S, Tomasik PJ. Prebiotics, probiotics, synbiotics, paraprobiotics and postbiotic compounds in IBD. Biomolecules. 2021;**11**:1903

[12] Gibson GR, Hutkins R, Sanders ME, Prescott SE, Reimer RA, Salminen SJ, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nature Reviews. Gastroenterology & Hepatology. 2017;**14**:491-502

[13] Cummings JH, Macfarlane GT. Gastrointestinal effects of prebiotics. The British Journal of Nutrition. 2002;**87**:S145-S151

[14] Van Loo J. The specificity of the interaction with intestinal bacterial fermentation by prebiotics determines

their physiological efficacy. Nutrition Research Reviews. 2004;**17**:89-98

[15] Benjamin JL, Hedin CR, Koutsoumpas A, Ng SC, McCarthy NE, Hart AL, et al. Randomised, double-blind, placebo-controlled trial of fructo-oligosaccharides in active Crohn's disease. Gut. 2011;**60**:923-929

[16] Manns MP, Bischoff SC. Effect of oral lactulose on clinical and immunohistochemical parameters in patients with inflammatory bowel disease: a pilot study. BMC Gastroenterol. 2007;**7**:36

[17] Kanauchi O, Mitsuyama K, Homma T, Takahama K, Fujiyama Y, Andoh A, et al. Treatment of ulcerative colitis patients by long-term administration of germinated barley foodstuff: Multi-center open trial. International Journal of Molecular Medicine. 2003;**12**:701-704

[18] Casellas F, Borruel N, Torrejón A, Varela E, Antolin M, Guarner F, et al. Oral oligofructose-enriched inulin supplementation in acute ulcerative colitis is well tolerated and associated with lowered faecal calprotectin. Alimentary Pharmacology & Therapeutics. 2007;**25**:1061-1067

[19] Hanai H, Kanauchi O, Mitsuyama K, Andoh A, Takeuchi K, Takayuki I, et al. Germinated barley foodstuff prolongs remission in patients with ulcerative colitis. International Journal of Molecular Medicine. 2004;**13**:643-647

[20] Hallert C, Kaldma M, Petersson BG. Ispaghula husk may relieve gastrointestinal symptoms in ulcerative colitis in remission. Scandinavian Journal of Gastroenterology. 1991;**26**:747-750

[21] Fernández-Bañares F, Hinojosa J, Sánchez-Lombraña JL, Navarro E, Martínez-Salmerón JF, García-Pugés A, et al. Randomized clinical trial of Plantago ovata seeds (dietary fiber) as compared with mesalamine in maintaining remission in ulcerative colitis. Spanish Group for the Study of Crohn's Disease and Ulcerative Colitis (GETECCU). The American Journal of Gastroenterology. 1999;**94**:427-433

[22] Azad MAK, Sarker M, Li T, Yin J. Probiotic species in the modulation of gut microbiota: An overview. BioMed Research International. 2018;**2018**:9478630

[23] Yoshimatsu Y, Mikami Y, Kanai T. Bacteriotherapy for inflammatory bowel disease. Inflammation and Regeneration. 2021;**41**:3

[24] Tamaki H, Nakase H, Inoue S, Kawanami C, Itani T, Ohana M, et al. Efficacy of probiotic treatment with Bifidobacterium longum 536 for induction of remission in active ulcerative colitis: A randomized, double-blinded, placebo-controlled multicenter trial. Digestive Endoscopy. 2016;**28**:67-74

[25] De Vrese M, Schrezenmeir J. Probiotics, prebiotics, and synbiotics. Advances in Biochemical Engineering/ Biotechnology. 2008;**111**:1-66

[26] Martín R, Miquel S, Ulmer J, Kechaou N, Langella P, Bermúdez-Humarán LG. Role of commensal and probiotic bacteria in human health: A focus on inflammatory bowel disease. Microbial Cell Factories. 2013;**12**:71

[27] Abraham BP, Quigley EMM. Probiotics in inflammatory bowel disease. Gastroenterology Clinics of North America. 2017;**46**:769-782

[28] Ghavami SB, Yadegar A, Aghdaei HA, Sorrentino D, Farmani M, Mir AS, et al. Immunomodulation and

generation of tolerogenic dendritic cells by probiotic bacteria in patients with inflammatory bowel disease. International Journal of Molecular Science. 2020;**21**:6266

[29] Jakubczyk D, Leszczynska K, Górska S. The effectiveness of probiotics in the treatment of inflammatory bowel disease (IBD): A critical review. Nutrients. 2020;**12**:1973

[30] Ekmekciu I, Von Klitzing E, Fiebiger U, Neumann C, Bacher P, Scheffold A, et al. The probiotic compound VSL#3 modulates mucosal, peripheral, and systemic immunity following murine broad-spectrum antibiotic treatment. Frontiers in Cellular and Infection Microbiology. 2017;**7**:1-19

[31] Zoppi G, Cinquetti M, Benini A, Bonamini E, Minelli EB. Modulation of the intestinal ecosystem by probiotics and lactulose in children during treatment with ceftriaxone. Current Therapeutic Research, Clinical and Experimental. 2001;**62**:418-435

[32] Wang L, Guo MJ, Gao Q, Yang JF, Yang L, Pang XL, et al. The effects of probiotics on total cholesterol. Medicine (United States). 2018;**97**:e9679

[33] Reid G, Bruce AW, Fraser N, Heinemann C, Owen J, Henning B. Oral probiotics can resolve urogenital infections. FEMS Immunology and Medical Microbiology. 2001;**30**:49-52

[34] Yoshimatsu Y, Yamada A, Furukawa R, Sono K, Osamura A, Nakamura K, et al. Effectiveness of probiotic therapy for the prevention of relapse in patients with inactive ulcerative colitis. World Journal of Gastroenterology. 2015;**21**:5985-5994

[35] Yılmaz I, Dolar ME, Özpınar H. Effect of administering kefir on the changes in fecal microbiota and symptoms of inflammatory ˙bowel disease: A randomized controlled trial. The Turkish Journal of Gastroenterology. 2019;**30**:242-253

[36] Shadnoush M, Hosseini RS, Khalilnezhad A, Navai L, Goudarzi H, Vaezjalali M. Effects of probiotics on gut microbiota in patients with inflammatory bowel disease: A double-blind, Placebo-controlled Clinical Trial. Korean Journal of Gastroenterology. 2015;**65**:215-221

[37] Palumbo VD, Romeo M, Marino Gammazza A, Carini F, Damiani P, Damiano G, et al. The long-term effects of probiotics in the therapy of ulcerative colitis: A clinical study. Biomedical Paper Medicine Faculty University. 2016;**160**:372-377

[38] Fan H, Du J, Liu X, Zheng WW, Zhuang ZH, Wang CD, et al. Effects of pentasa-combined probiotics on the microflora structure and prognosis of patients with inflammatory bowel disease. The Turkish Journal of Gastroenterology. 2019;**30**:680-685

[39] Su H, Kang Q, Wang H, Yin H, Duan L, Liu Y, et al. Effects of glucocorticoids combined with probiotics in treating Crohn's disease on inflammatory factors and intestinal microflora. Experimental and Therapeutic Medicine. 2018;**16**:2999-3003

[40] Bjarnason I, Sission G, Hayee B. A randomised, double-blind, placebo-controlled trial of a multi-strain probiotic in patients with asymptomatic ulcerative colitis and Crohn's disease. Inflammopharmacology. 2019;**27**:465-473

[41] Fedorak RN, Feagan BG, Hotte N, Leddin D, Dieleman LA, Petrunia DM, et al. The probiotic VSL#3 has anti-inflammatory effects and could reduce

endoscopic recurrence after surgery for Crohn's disease. Clinical Gastroenterology and Hepatology. 2015;**13**:928-935

[42] Matsuoka K, Uemura Y, Kanai T, Kunisaki R, Suzuki Y, Yokoyama K, et al. Efficacy of Bifidobacterium breve fermented milk in maintaining remission of ulcerative colitis. Digestive Diseases and Sciences. 2018;**63**:1910-1919

[43] Astó E, Méndez I, Audivert S, Farran-Codina A, Espadaler J. The efficacy of probiotics, prebiotic inulin-type fructans, and synbiotics in human ulcerative colitis: A systematic review and meta-analysis. Nutrients. 2019;**11**:293

[44] Zhang XF, Guan XX, Tang YJ, Sun JF, Wang XK, Wang WD, et al. Clinical effects and gut microbiota changes of using probiotics, prebiotics or synbiotics in inflammatory bowel disease: A systematic review and meta-analysis. European Journal of Nutrition. 2021;**60**:2855

[45] Jia K, Tong X, Wang R, Song X. The clinical effects of probiotics for inflammatory bowel disease: A meta-analysis. Medicine. 2018;**97**:e13792

[46] Puvvada SR, Luvsannyam E, Patel D, Hassan Z, Hamid P. Probiotics in inflammatory bowel disease: Are we back to square one? Cureus. 2020;**12**:e10247

[47] Dore MP, Bibbò S, Fresi G, Bassotti G, Pes GM. Side effects associated with probiotic use in adult patients with inflammatory bowel disease: A systematic review and meta-analysis of randomized controlled trials. Nutrients. 2019;**11**:2913

[48] Dore MP, Rocchi C, Longo NP, Scanu AM, Vidili G, Padedda F, et al. Effect of probiotic use on adverse events in adult patients with inflammatory bowel disease: A Retrospective Cohort Study. Probiotics Antimicrobial Proteins. 2020;**12**:152-159

[49] Mishra J, Stubbs M, Kuang L, Vara N, Kumar P, Kumar N. Inflammatory bowel disease therapeutics: A focus on probiotic engineering. Mediators of Inflammation Volume. 2022;**962**:15

[50] Glassner KL, Abraham BP, Quigley EMM. The microbiome and inflammatory bowel disease. The Journal of Allergy and Clinical Immunology. 2020s;**145**:16-27

[51] Goh YJ, Barrangou R. Harnessing CRISPR-Cas systems for precision engineering of designer probiotic lactobacilli. Current Opinion in Biotechnology. 2019;**56**:163-171

[52] Hamady ZZ, Scott N, Farrar MD, et al. Xylan-regulated delivery of human keratinocyte growth factor-2 to the inflamed colon by the human anaerobic commensal bacterium Bacteroides ovatus. Gut. 2010;**59**(4):461-469

[53] Del Carmen S, De Leblanc AD, Perdigon G, et al. Evaluation of the anti-inflammatory effect of milk fermented by a strain of IL-10-producing Lactococcus lactis using a murine model of Crohn's disease. Journal of Molecular Microbiology and Biotechnology. 2011;**21**:138-146

[54] Steidler L, Hans W, Schotte L, et al. Treatment of murine colitis by Lactococcus lactis Secreting interleukin-10. Science. 2000;**289**(5483):1352-1355

[55] Veenbergen S, Li P, Raatgeep HC, et al. IL-10 signaling in dendritic cells controls IL-1β-mediated IFNγ secretion by human CD4+ T cells: Relevance to

inflammatory bowel disease. Mucosal Immunology. 2019;**12**(5):1201-1211

[56] Friedrich M, Pohin M, Powrie F. Cytokine networks in the pathophysiology of inflammatory bowel disease. Immunity. 2019;**50**:992-1006

[57] Barra M, Danino T, Garrido D. Engineered probiotics for detection and treatment of inflammatory intestinal diseases. Frontiers in Bioengineering and Biotechnology. 2020;**8**:265

[58] Lavasani S, Dzhambazov B, Nouri M, et al. A novel probiotic mixture exerts a therapeutic effect on experimental autoimmune encephalomyelitis mediated by IL-10 producing regulatory T cells. PLoS One. 2010;**5**:e9009

[59] Andrews C, McLean MH, Durum SK. Interleukin-27 as a novel therapy for inflammatory bowel disease: A critical review of the literature. Inflammatory Bowel Diseases. 2016;**22**:2255-2264

[60] McLean MH, Andrews C, Hanson ML, et al. Interleukin-27 is a potential rescue therapy for acute severe colitis through interleukin-10-dependent, T-cell-independent attenuation of colonic mucosal innate immune responses. Inflammatory Bowel Diseases. 2017;**23**:1983-1995

[61] Hanson ML, Hixon JA, Li W, et al. Oral delivery of IL-27 recombinant bacteria attenuates immune colitis in mice. Gastroenterology. 2014;**146**:210-221

[62] Al-Meghaiseeb ES, Al-Robayan AA, Al-Otaibi MM, Arfin M, Al-Asmari AK. Association of tumor necrosis factor-alpha and -beta gene polymorphisms in inflammatory bowel disease. Journal of Inflammation Research. 2016;**9**:133-140

[63] Holmgren J, Czerkinsky C. Mucosal immunity and vaccines. Nature Medicine. 2005;**11**:S45-S53

[64] Jiang B, Li Z, Ou B, Duan Q, Zhu G. Targeting ideal oral vaccine vectors based on probiotics: A systematical view. Applied Microbiology and Biotechnology. 2019;**103**:3941-3953

[65] Isolauri E, Majamaa H, Arvola T, Rantala I, Virtanen E, Arvilommi H. Lactobacillus casei strain GG reverses increased intestinal permeability induced by cow milk insuckling rats. Gastroenterology. 1993;**105**:1643-1650

[66] Mathipa MG, Thantsha MS. Probiotic engineering: Towards development of robust probiotic strains with enhanced functional properties and for targeted control of enteric pathogens. Gut Pathogens. 2017;**9**:28

[67] Akutko K, Stawarski A. Probiotics, prebiotics and synbiotics in inflammatory bowel diseases. Journal of Clinical Medicine. 2021;**10**:2466

[68] Wasilewski A, Zielinska M, Storr M, Fichna J. Beneficial effects of probiotics, prebiotics, synbiotics, and psychobiotics in inflammatory bowel disease. Inflammatory Bowel Diseases. 2015;**21**:1674-1682

[69] Steed H, Macfarlane GT, Blackett KL, Bahrami B, Reynolds N, Walsh SV, et al. Clinical trial: The microbiological and immunological effects of synbiotic consumption—A randomized double-blind placebo-controlled study in active Crohn's disease. Alimentary Pharmacology & Therapeutics. 2010;**32**:872-883

[70] Furrie E, Macfarlane S, Kennedy A, Cummings JH, Walsh SV, O'neil DA, et al. Synbiotic therapy (Bifidobacterium longum/Synergy 1) initiates resolution of inflammation in patients with active ulcerative colitis: A randomised controlled pilot trial. Gut. 2005;**54**:242-249

[71] Chermesh I, Tamir A, Reshef R, Chowers Y, Suissa A, Katz D, et al. Failure of Synbiotic 2000 to prevent postoperative recurrence of Crohn's disease. Digestive Diseases and Sciences. 2007;**52**:385-389

[72] Fujimori S, Gudis K, Mitsui K, Seo T, Yonezawa M, Tanaka S, et al. A randomized controlled trial on the efficacy of synbiotic versus probiotic or prebiotic treatment to improve the quality of life in patients with ulcerative colitis. Nutrition. 2009;**25**:520-525

[73] Ishikawa H, Matsumoto S, Ohashi Y, Imaoka A, Setoyama H, Umesaki Y, et al. Beneficial effects of probiotic bifidobacterium and galacto-oligosaccharide in patients with ulcerative colitis: A randomized controlled study. Digestion. 2011;**84**:128-133

[74] Floch MH. Probiotic Safety and Risk Factors. Journal of Clinical Gastroenterology. 2013;**47**:375-376

[75] Vahabnezhad E, Mochon AB, Wozniak LJ, Ziring DA. Lactobacillus bacteremia associated with probiotic use in a pediatric patient with ulcerative colitis. Journal of Clinical Gastroenterology. 2013;**47**:437-439

[76] Martín R, Langella P. Emerging health concepts in the probiotics field: Streamlining the definitions. Frontiers in Microbiology. 2019;**10**:1047

[77] De Almada CN, de Almada CN, de Sant'Ana AS. Paraprobiotics as potential agents for improving animal health. In: Probiotics and Prebiotics in Animal Health and Food Safety. Berlin/Heidelberg, Germany: Springer International Publishing; 2018. pp. 247-268

[78] Akter S, Jung J-HP, Jung HK. Potential health-promoting benefits of paraprobiotics, inactivated probiotic cells. Journal of Microbiology Biotechnology. 2020;**30**:477-481

[79] De Almada CN, Almada CN, Martinez RCR, Sant'Ana AS. Paraprobiotics: Evidences on their ability to modify biological responses, inactivation methods and perspectives on their application in foods. Trends in Food Science and Technology. 2016;**58**:96-114

[80] Barros CP, Guimarães JT, Esmerino EA, Duarte MCK, Silva MC, Silva R, et al. Paraprobiotics and postbiotics: Concepts and potential applications in dairy products. Current Opinion in Food Science. 2020;**32**:1-8

[81] Sharma M, Shukla G. Metabiotics: One step ahead of probiotics; an insight into mechanisms involved in anticancerous effect in colorectal cancer. Frontiers in Microbiology. 2016;**7**:1940

[82] Fang SB, Shih HY, Huang CH, Li LT, Chen CC, Fang HW. Live and heat-killed Lactobacillus rhamnosus GG upregulate gene expression of pro-inflammatory cytokines in 5-fluorouracil-pretreated Caco-2 cells. Supportive Care in Cancer. 2014;**22**:1647-1654

[83] Ryu YH, Baik JE, Yang JS, Kang SS, Im J, Yun CH, et al. Differential immunostimulatory effects of gram-positive bacteria due to their lipoteichoic acids. International Immunopharmacology. 2009;**9**:127-133

[84] Teame T, Wang A, Xie M, Zhang Z, Yang Y, Ding Q, et al. Paraprobiotics and postbiotics of probiotic lactobacilli, their positive effects on the host and action mechanisms: A review. Frontiers in Nutrition. 2020;**7**:570344

[85] Shenderov BA. Metabiotics: Novel idea or natural development of probiotic

conception. Microbial Ecology in Health and Disease. 2013;**24**

[86] Oleskin AV, Shenderov BA. Microbial Communication and Microbiota-Host Interactivity: Neurophysiological, Biotechnological, and Biopolitical Implications. Hauppauge, NY, USA: Nova Science Publishers; 2020

[87] Macfarlane S, Macfarlane GT. Regulation of short-chain fatty acid production. The Proceedings of the Nutrition Society. 2003;**62**:67-72

[88] Russo E, Giudici F, Fiorindi C, Ficari F, Scaringi S, Amedei A. Immunomodulating activity and therapeutic effects of short chain fatty acids and tryptophan post-biotics in inflammatory bowel disease. Frontiers in Immunology. 2019;**10**:2754

[89] Topping DL, Clifton PM. Short-chain fatty acids and human colonic function: Roles of resistant starch and nonstarch polysaccharides. Physiological Reviews. 2001;**81**:1031-1064

[90] Poul EL, Loison C, Struyf S, Springael J-Y, Lannoy V, Decobecq M-E, et al. Functional characterization of human receptors for short chain fatty acids and their role in polymorphonuclear cell activation. The Journal of Biological Chemistry. 2003;**278**:25481-25489

[91] Canani RB, di Costanzo M, Leone L, Pedata M, Meli R, Calignano A. Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. World Journal of Gastroenterology. 2011;**17**:1519-1528

[92] Scheppach W, Weiler F. The butyrate story: Old wine in new bottles? Current Opinion in Clinical Nutrition and Metabolic Care. 2004;**7**:563-567

[93] Brummer R-JM. Effect of butyrate enemas on inflammation and antioxidant status in the colonic mucosa of patients with ulcerative colitis in remission. Clinical Nutrition. 2010;**29**:738-744

[94] Vernia P, Annese V, Bresci G, D'Albasio G, D'Incà R, Giaccari S, et al. Topical butyrate improves efficacy of 5-ASA in refractory distal ulcerative colitis: Results of a Multicentre Trial. European Journal of Clinical Investigation. 2003;**33**:244-248

[95] Di Sabatino A, Morera R, Ciccocioppo R, Cazzola P, Gotti S, Tinozzi FP, et al. Oral butyrate for mildly to moderately active Crohn's disease. Alimentary Pharmacology & Therapeutics. 2005;**22**:789-794

[96] Matsumoto N, Riley S, Fraser D, Al-Assaf S, Ishimura E, Wolever T, et al. Butyrate modulates TGF-B1 generation and function: Potential renal benefit for Acacia (Sen) supergumtm (Gum Arabic)? Kidney International. 2006;**69**:257-265

[97] Wanders D, Graff EC, Judd RL. Effects of high fat diet on GPR109A and GPR81 gene expression. Biochemical and Biophysical Research Communications. 2012;**425**:278-283

[98] Singh N, Gurav A, Sivaprakasam S, Brady E, Padia R, Shi H, et al. Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate. Suppresses Colonic Inflammation and Carcinogenesis. Immunity. 2014;**40**:128-139

[99] Al-Lahham SH, Peppelenbosch MP, Roelofsen H, Vonk RJ, Venema K. Biological effects of propionic acid in humans; Metabolism, potential applications and underlying mechanisms. Biochimica Biophysica Acta. 1801;**2010**:1175-1183

[100] Tedelind S, Westberg F, Kjerrulf M, Vidal A. Anti-inflammatory properties of the short-chain fatty acids acetate and propionate: A study with relevance to inflammatory bowel disease. World Journal of Gastroenterology. 2007;**13**:2826-2832

[101] Perry RJ, Peng L, Barry NA, Cline GW, Zhang D, Cardone RL, et al. Acetate mediates a microbiome–brain–β-cell axis to promote metabolic syndrome. Nature. 2016;**534**:213-217

[102] Macia L, Tan J, Vieira AT, Leach K, Stanley D, Luong S, et al. Metabolite-sensing receptors GPR43 and GPR109A facilitate dietary fibre-induced gut homeostasis through regulation of the inflammasome. Nature Communications. 2015;**6**:1-15

[103] Vernia P, Marcheggiano A, Caprilli R, Frieri G, Corrao G, Valpiani D, et al. Short-chain fatty acid topical treatment in distal ulcerative colitis. Alimentary Pharmacology & Therapeutics. 1995;**9**:309-313

[104] Lührs H, Gerke T, Müller JG, Melcher R, Schauber J, Boxberger F, et al. Butyrate inhibits NF-KB activation in lamina propria macrophages of patients with ulcerative colitis. Scandinavian Journal of Gastroenterology. 2002:458-466

[105] Senagore AJ, MacKeigan JM, Scheider M, Ebrom JS. Short-chain fatty acid enemas: A cost-effective alternative in the treatment of nonspecific proctosigmoiditis. Diseases of the Colon and Rectum. 1992;**35**:923-927

[106] Scheppach W, Sommer H, Kirchner T, Paganelli G-M, Bartram P, Christl S, et al. Effect of butyrate enemas on the colonic mucosa in distal ulcerative colitis. Gastroenterology. 1992;**103**:51-56

[107] Scheppach W. Treatment of distal ulcerative colitis with short-chain fatty acid enemas. A Placebo-Controlled Trial.German Austrian SCFA Study Group. Digestive Disease Science. 1996;**41**:2254-2259

[108] Steinhart AH, Hiruki T, Brzezinski A, Baker JP. Treatment of left-sided ulcerative colitis with butyrate enemas: A Controlled Trial. Alimentary Pharmacology & Therapeutics. 1996;**10**:729-736

[109] Breuer RI, Soergel KH, Lashner BA, Christ ML, Hanauer SB, Vanagunas A, et al. Short chain fatty acid rectal irrigation for left-sided ulcerative colitis: A Randomised, Placebo Controlled Trial. Gut. 1997;**40**:485

[110] Schiering C, Wincent E, Metidji A, Iseppon A, Li Y, Potocnik AJ, et al. Feedback control of AHR signalling regulates intestinal immunity. Nature. 2017;**542**:242-245

[111] Levin AD, van den Brink GR. Selective inhibition of mucosal serotonin as treatment for IBD? Gut. 2014;**63**:866-867

[112] Gao J, Xu K, Liu H, Liu G, Bai M, Peng C, et al. Impact of the gut microbiota on intestinal immunity mediated by tryptophan metabolism. Frontiers in Cellular and Infection Microbiology. 2018;**8**:13

[113] Nikolaus S, Schulte B, Al-Massad N, Thieme F, Schulte DM, Bethge J, et al. Increased tryptophan metabolism is associated with activity of inflammatory bowel diseases. Gastroenterology. 2017;**153**:1504-1516

[114] Wolf AM, Wolf D, Rumpold H, Moschen AR, Kaser A, Obrist P, et al. Overexpression of indoleamine 2,3-dioxygenase in human inflammatory

bowel disease. Clinical Immunology. 2004;**113**:47-55

[115] Lamas B, Richard ML, Leducq V, Pham H-P, Michel M-L, da Costa G, et al. CARD9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands. Nature Medicine. 2016;**22**:598-605

[116] Cervantes-Barragan L, Chai JN, Tianero MD, di Luccia B, Ahern PP, Merriman J, et al. Lactobacillus Reuteri induces gut intraepithelial CD4+CD8αα+ T Cells. Science. 2017;**357**:806-810

[117] Lee J-Y, Cevallos SA, Byndloss MX, Tiffany CR, Olsan EE, Butler BP, et al. High-fat diet and antibiotics cooperatively impair mitochondrial bioenergetics to trigger dysbiosis that exacerbates pre-inflammatory bowel disease. Cell Host Microbe. 2020;**28**:273-284

[118] Oka A, Sartor RB. Microbial-based and microbial-targeted therapies for inflammatory bowel diseases. Digestive Diseases and Sciences. 2020;**65**:757-788

[119] Maccaferri S, Vitali B, Klinder A, Kolida S, Ndagijimana M, Laghi L, et al. Rifaximin modulates the colonic microbiota of patients with Crohn's disease: An in vitro approach using a continuous culture colonic model system. The Journal of Antimicrobial Chemotherapy. 2010;**65**:2556-2565

[120] Bücker R, Schulz E, Günzel D, Bojarski C, Lee I-FM, John LJ, et al. α-Haemolysin of Escherichia coliin IBD: A potentiator of inflammatory activity in the colon. Gut. 2014;**63**:1893-1901

[121] Lev-Tzion R, Ledder O, Shteyer E, Tan MLN, Uhlig HH, Turner D. Oral vancomycin and gentamicin for treatment of very early onset inflammatory bowel disease. Digestion. 2017;**95**:310-313

[122] Townsend CM, Parker CE, MacDonald JK, Nguyen TM, Jairath V, Feagan BG, et al. Antibiotics for induction and maintenance of remission in Crohn's disease. Cochrane Database of Systematic Reviews. 2019;**2**:CD012

[123] Sprockett D, Fischer N, Boneh RS, Turner D, Kierkus J, Sladek M, et al. Treatment-specific composition of the gut microbiota is associated with disease remission in a pediatric Crohn's disease Cohort. Inflammatory Bowel Diseases. 2019;**25**:1927-1938

[124] Zhang L, Ma X, Liu P, Ge W, Hu L, Zuo Z, et al. Treatment and mechanism of fecal microbiota transplantation in mice with experimentally induced ulcerative colitis. Experimental Biology and Medicine (Maywood, N.J.). 2021;**246**(13):1563-1575

[125] Imdad A, Nicholson MR, Tanner-Smith EE, Zackular JP, Gomez-Duarte OG, Beaulieu DB, et al. Fecal transplantation for treatment of inflammatory bowel disease. Cochrane Database of Systematic Reviews. 2018;**11**:CD012

[126] Fang H, Fu L, Wang J. Protocol for fecal microbiota transplantation in inflammatory bowel disease: A systematic review and meta-analysis. BioMed Research International. 2018;**894**:11

[127] Sokol H, Landman C, Seksik P, et al. Fecal microbiota transplantation to maintain remission in Crohn's disease: A pilot randomized controlled study. Microbiome. 2020;**8**:12

[128] Santiago-Rodriguez T, Hollister E. Human virome and disease: High-throughput sequencing for virus

discovery, identification of phage-bacteria dysbiosis and development of therapeutic approaches with emphasis on the human gut. Viruses. 2019;**11**:656

[129] Pérez-Brocal V, García-López R, Nos P, Beltrán B, Moret I, Moya A. Metagenomic analysis of Crohn's disease patients identifies changes in the virome and microbiome related to disease status and therapy, and detects potential interactions and biomarkers. Inflammatory Bowel Diseases. 2015;**21**:2515-2532

[130] Fernandes MA, Verstraete SG, Phan TG, Deng X, Stekol E, LaMere B, et al. Enteric virome and bacterial microbiota in children with ulcerative colitis and Crohn Disease. Journal of Pediatric Gastroenterology and Nutrition. 2019;**68**:30-36

[131] Duerkop BA, Kleiner M, Paez-Espino D, Zhu W, Bushnell B, Hassell B, et al. Murine colitis reveals a disease-associated bacteriophage community. Nature Microbiology. 2018;**3**:11023-11031

[132] Maronek M, Link R, Ambro L, Gardlik R. Phages and their role in gastrointestinal disease: Focus on inflammatory bowel disease. Cell. 2020;**9**:1013

[133] Zhang L, Hou X, Sun L, He T, Wei R, Pang M, et al. Corrigendum: *Staphylococcus aureus* bacteriophage suppresses LPS-induced inflammation in MAC-T bovine mammary epithelial cells. Frontiers in Microbiology. 2018;**9**:3389

[134] Górski A, Bollyky PL, Przybylski M, Borysowski J, Miedzybrodzki R, Jonczyk-Matysiak E, et al. Perspectives of phage therapy in non-bacterial infections. Frontiers in Microbiology. 2019;**9**:1

[135] Lemire S, Yehl KM, Lu TK. Phage-based applications in synthetic biology. Annual Review in Virology. 2018;**5**:453-476

[136] Chehoud C, Dryga A, Hwang Y, Nagy-Szakal D, Hollister EB, Luna RA, et al. Transfer of viral communities between human individuals during fecal microbiota transplantation. mBio. 2016;**7**:1-8

[137] Broecker F, Russo G, Klumpp J, Moelling K. Stable core virome despite variable microbiome after fecal transfer. Gut Microbes. 2017;**8**:214-220

[138] Ott SJ, Waetzig GH, Rehman A, Moltzau-Anderson J, Bharti R, Grasis JA, et al. Efficacy of sterile fecal filtrate transfer for treating patients with clostridium difficile infection. Gastroenterology. 2017;**152**:799-811

[139] Galtier MA. Bacteriophages targeting adherent invasive Escherichia coli strains as a promising new treatment for Crohn's disease. Journal of Crohn's & Colitis. 2017;**11**:840-847

[140] Speck P, Smithyman A. Safety and efficacy of phage therapy via the intravenous route. FEMS Microbiology Letters. 2016;**363**:1-6

[141] Malik DJ, Sokolov IJ, Vinner GK, Mancuso F, Cinquerrui S, Vladisavljevic GT, et al. Formulation, stabilisation and encapsulation of bacteriophage for phage therapy. Advances in Colloid and Interface Science. 2017;**249**:100-133

[142] McCallin S, Sarker SA, Sultana S, Oechslin F, Brssow H. Metagenome analysis of Russian and Georgian Pyophage cocktails and a placebo-controlled safety trial of single phage versus phage cocktail in healthy Staphylococcus aureus carriers.

Environmental Microbiology. 2018;**20**:3278-3293

[143] Rhoads DD, Wolcott RD, Kuskowski MA, Wolcott BM, Ward LS, Sulakvelidze A. Bacteriophage therapy of venous leg ulcers in humans: Results of a phase I safety trial. Journal of Wound Care. 2009;**18**:237-243