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ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Dr. Naoki Hashimoto was awarded his medical degree from Kobe University in 1975 and his PhD from Hyogo Medical College in 1984. Over the last 10 years, his scientific interest has remained focused on topics related to reflux of duodenal contents inducing esophageal carcinogenesis, with his research efforts including both experimental and clinical approaches. His practical expertise encompasses biomedical imaging, surgical treatment and chemoradiotherapy for advanced esophageal cancer, and he practices in the Kindai University's Department of Surgery. He is the recipient of many academic honors, from such esteemed groups as European Conference on General Thoracic Surgery in 2012 and World Organization for Specialized Studies of Diseases of the Esophagus (OESO) in 2013 and 2015. His academic career embodies a continual pursuit towards conducting more innovative, translational and enduring research.

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Regulation of the intestinal microbiota: An emerging therapeutic strategy for inflammatory bowel disease

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Abstract

The rapid development of metagenomics, metabolomics, and metatranscriptomics provides novel insights into the intestinal microbiota factors linked to inflammatory bowel disease (IBD). Multiple microorganisms play a role in intestinal health; these include bacteria, fungi, and viruses that exist in a dynamic balance to maintain mucosal homeostasis. Perturbations in the intestinal microbiota disrupt mucosal homeostasis and are closely related to IBD in humans and colitis in mice. Therefore, preventing or correcting the imbalance of microbiota may serve as a novel prevention or treatment strategy for IBD. We review the most recent evidence for direct or indirect interventions targeting intestinal microbiota for treatment of IBD in order to overcome the current limitations of IBD therapies and shed light on personalized treatment options.

Key words: Inflammatory bowel disease; Pro/Prebiotics; Fecal microbiota transplantation; Herbal medicines; Clinical application

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Core tip: In this review, we explore therapies targeting intestinal microbiota, such as fecal bacteria transplantation, pro/prebiotics, and herbal medicinal products, that represent effective therapeutic options to control and slow the progression of inflammatory bowel disease (IBD). We also discuss some challenges and controversies in relation to these emerging therapeutic strategies. This has direct inspiration for researchers to overcome the current limitations of IBD therapies and shed light on personalized treatment options.

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INTRODUCTION

Inflammatory bowel disease (IBD), which has been listed by the World Health Organization as one of the most refractory diseases, includes ulcerative colitis (UC) and Crohn's disease (CD) and shows a continually increasing incidence^[1]. Although genetic, epigenetics, immunological, microbial, and environmental factors are involved in the etiology of IBD, none have been identified as the explicit and direct cause of IBD^[2,3]. A generally accepted perspective is that the gut microbiota is affected by environmental factors (*e.g.*, diet, medications, smoking, and contaminants) that further impact the host immune response, contributing to the occurrence and development of IBD^[4]. It is thus clear that gut microbiota represent a link between environmental factors and the immune response^[5]. Recent studies have found that lack of intestinal microorganisms during early childhood influences the maturation and tolerance of the intestinal immune system, thus increasing IBD risk in adulthood^[6]. In addition, the defects of several pattern recognition receptors genes, such as toll-like receptors and nod-like receptors genes, lead to disturbances of innate immunity, which can ultimately reduce the host tolerance against intestinal microorganisms^[7]. Therefore, healthy gut microbiota are vital for intestinal health.

It has been confirmed that the intestine has rich microbial abundance, which includes enteric bacteria (99.1% of the gut microflora), archaea (the majority of the remainder), as well as only 0.1% of fungi and viruses^[8,9]. The total number of microorganisms present is more than 10 times the total number of human cells^[10]. The intestinal microbiota is dominated by *Firmicutes* (49%-76%) and *Bacteroidetes* (16%-23%) phyla, while others are less abundant bacterial phyla. The main fungal microbiota in intestinal tract are *Ascomycota* and *Basidiomycota* phyla^[11]. The enteric virome includes all nucleic acids (DNA and/or RNA) that mapped to viral genomes from fecal samples or virus-like particles rooted in fecal samples^[12]. With regard to the enteric virome, eukaryotic viruses, bacteriophages, and pathogenic viruses are present in the gastrointestinal tract^[13]. However, in recent years, increasing evidence suggests that the intestinal microbial composition is significantly altered in IBD patients compared with that in healthy subjects^[14]. Therefore, regulation of the disturbed intestinal microbiota may represent a new therapeutic strategy for IBD.

Classical therapeutic approaches for IBD are varied, and include anti-inflammatory, immunosuppressive, and biologic therapies, largely applied and developed in clinical practice^[15]. IBD is a persistent and recurrent disease and requires long-term treatment, which often results in drug-induced side effects. Furthermore, numerous IBD patients do not respond to clinically approved drugs^[16], necessitating the development of novel therapies or complementary and alternative medicine for IBD. It is worth mentioning that, with the rapid advancement in metagenomics, complementary and alternative therapies for IBD based on modulation of gut microbiota have developed rapidly and preliminary achievements have been reported^[17]. Pro/prebiotics, herbal medicinal products, and fecal bacteria transplantation (FMT) are emerging therapeutic strategies for IBD that target intestinal microbiota in a direct or indirect way, thus benefiting intestinal health^[18].

In this review, we explore therapies targeting intestinal microbiota, such as FMT, pro/prebiotics, and herbal medicinal products, that may represent effective therapeutic options to control and slow the progression of IBD. We also discuss some clinical applications and where to place more focus on these emerging therapeutic strategies (Figure 1).

THERAPEUTIC STRATEGIES TARGETING INTESTINAL MICROBIOTA

Probiotics: Live bacterial biotherapeutics

Probiotics were first proposed in 1908 by Nobel laureate Eile Metchnikoff, who also defined the first probiotic agents, lactic acid bacteria, which exert the physiological

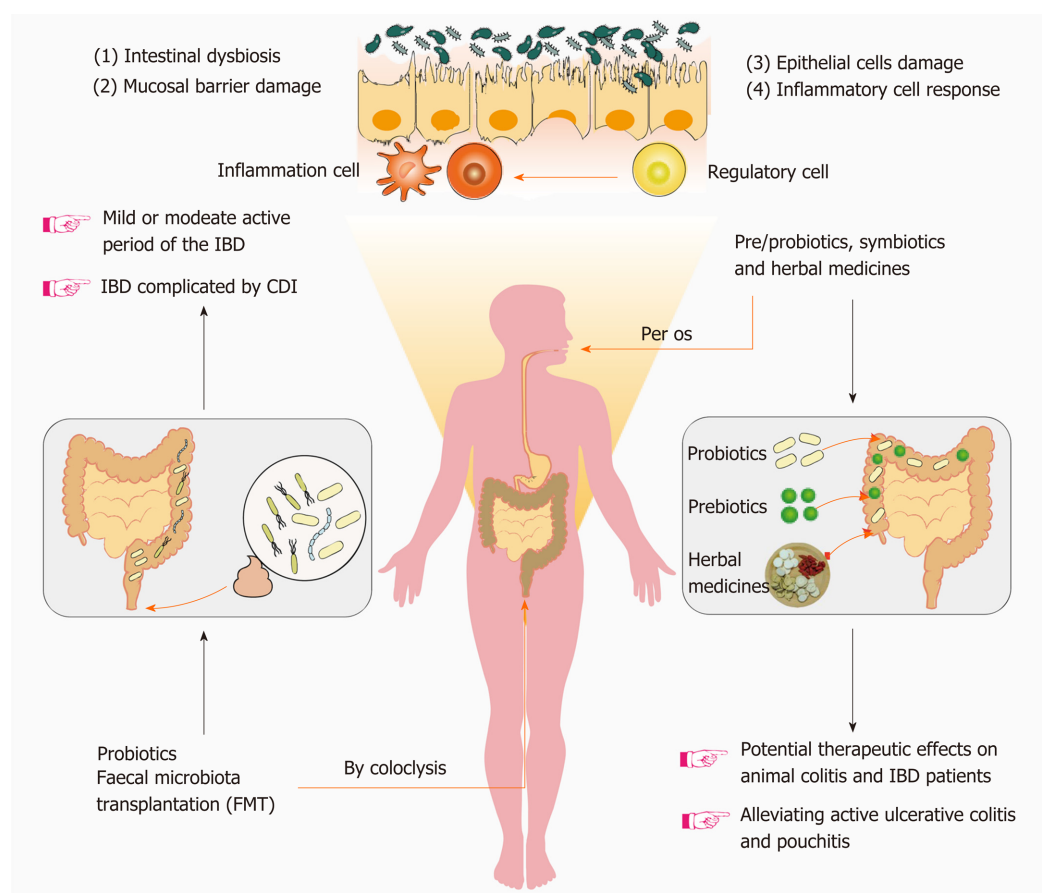


Figure 1 Regulation of intestinal microbiota as a therapeutic strategy for inflammatory bowel disease. Microbe-based therapies for inflammatory bowel disease (IBD) can be divided into two categories, namely: Direct regulation of microbiota [probiotics and fecal bacteria transplantation (FMT)] and indirect regulation (prebiotics and herbal medicines). Intestinal dysbiosis, mucosal barrier damage, epithelial cell damage and inflammatory cell response often coexist in patients with IBD. However, FMT has now been used to test the treatment of mild or moderate active period of IBD as well as IBD patients complicated by *Clostridium difficile* infection. Pre/probiotics, symbiotics and herbal medicines display potential therapeutic effects in animal colitis as well as certain IBD patients, especially for active ulcerative colitis. Hence, it is necessary to screen and design personalized microbiota-based therapies in order to enhance the specificity and selectivity of the therapeutic strategy targeting intestinal microbiota. IBD: Inflammatory bowel disease; FMT: Fecal bacteria transplantation; CDI: *Clostridium difficile* infection.

effects of inhibiting “intestinal autotoxicity”, delaying intestinal aging, and eliciting beneficial effects on human health^[19]. Since then, the concept of intestinal probiotics has been continuously developing, and new probiotic strains are still being identified. The latest scientific definition of probiotics, *i.e.* “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” was advanced in 2014^[20]. Probiotic strains discovered to date mostly belong to the phylum *Firmicutes* and include the genera *Aerococcus*, *Enterococcus*, *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Oenococcus*, *Pediococcus*, *Streptococcus*, *Carnobacterium*, *Tetragenococcus*, *Vagococcus*, and *Weissella*; as well as *Bifidobacterium* genera attributed to *Actinobacteria*, and *Saccharomyces* belonging to *Eumycota*^[21]. *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* strains are probiotics that have a long history of application and have attracted much interest. Furthermore, with the evolution and innovations in sequencing technology, researchers have discovered novel probiotic strains referred to as the “next-generation of probiotics”, of which include *Akkermansia muciniphila*, *Propionibacterium* spp., and *Roseburia* spp., with promising applications^[22,23].

However, the clinical application of probiotic preparations is still very limited, and their scope of application and effectiveness are still being investigated^[24]. As a mixture of high-concentration probiotic preparations, VSL#3 comprises 8 live lyophilized bacterial strains, namely *Streptococcus thermophilus*, 3 strains of *Bifidobacterium* (*B. longum*, *B. breve*, and *B. infantis*) and 4 strains of *Lactobacilli* (*L. paracasei*, *L. plantarum*, *L. acidophilus*, and *L. delbrueckii* subspecies *bulgaricus*)^[25]. VSL#3 has long been used in clinical settings for the treatment and remission of IBD. A study confirmed that VSL#3 achieved remission in patients with mild-to-moderately active UC, with high safety and efficacy^[26]. Moreover, in a recent systematic meta-analysis, VSL#3 also demonstrated efficacy in alleviating active UC and pouchitis, and could effectively

protect against its recurrence in a static period of disease; however, its potential utility in CD patients has not been demonstrated^[27,28]. The precise effects of probiotics in the intestinal tract are still unclear.

Elucidation of the mechanisms by which probiotic bacteria exert protective effects in IBD are crucial for identifying optimal treatment strategies. The potential effects of probiotics on the intestine may be classified into 4 categories: (1) Probiotics regulate immune responses and inhibit inflammatory reactions by mediating several signal transduction pathways, such as the Toll-like receptor signaling pathway^[29,30]; (2) Probiotics inhibit or directly eliminate enteropathogenic microorganisms by competing for nutrients and intestinal-epithelium adhesion sites, and secreting antimicrobial substances^[30,31]; (3) Probiotics help maintain intestinal epithelial homeostasis by promoting tight junction (TJ) formation, boosting mucus production, and anti-epithelial cell apoptosis^[31]; and (4) Probiotics can directly impact the metabolic profile of intestinal microbiota and the host, thus promoting the regulation of colonic cell proliferation and the clearance of hazardous substances from the intestinal tract^[32]. Diverse antimicrobial mechanisms and substances are involved, *e.g.*, lactic acid can disrupt enteropathogenic-microorganism metabolism by decreasing luminal pH, bacteriocins can damage cytoplasmic membrane formation, and microcins disturb the macromolecular synthetic pathways^[33]. An antimicrobial protease encoded by *Lactobacillus paracasei* *partP*, lactocepin, which can selectively degrade pro-inflammatory chemokine IP-10 level^[34].

Prebiotics: Nourishing probiotic preparations

Nondigestible oligosaccharides, in particular fructo-oligosaccharides, have been used to promote health for a long time. Prebiotics were first defined as a “non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria already resident in the colon” in 1995^[35]. Since then and particularly between 2001 and 2014, the concept and meaning of prebiotics has been extended; the latest and most widely accepted definition is “a substrate that is selectively utilized by host microorganisms conferring a health benefit”^[36]. A large category of prebiotics are oligosaccharides, which include cereal-derived arabinoxylans and arabinoxylan, fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), glucans, gluco/xylo-oligosaccharides, isomalto-oligosaccharides, poly-dextrose, soya bean oligosaccharides, and *trans*-galacto-oligosaccharides. Others include inulin and lactulose, classified as non-digestible carbohydrates^[21,37,38]. A third type of emerging, and increasingly popular, prebiotic class is represented by plant polyphenols, ellagitannins, and proanthocyanidins; 90%-95% of these cannot be absorbed or utilized in the small intestine. However, in the colon, they can undergo a process of biotransformation by intestinal microorganisms and produce ingredients that are beneficial to health^[39,40]. Among these, the most widely studied prebiotics, whose biological functions are best understood, are inulin, FOS, GOS, and lactulose.

The effect of prebiotics is to stimulate several microbial groups, and to increase not only the abundance of commensal *Lactobacillus* and/or *Bifidobacterium*, but also other beneficial taxa, such as *Roseburia*, *Eubacterium* and *Faecalibacterium* spp^[19,36]. A recent study found that inulin causes a shift in the intestinal microecology, manifesting in an increased abundance of *Bifidobacterium* and *Anaerostipes*, and a decreased abundance of *Bilophila*^[41]. Several studies have attempted to explain how prebiotics alter the intestinal microbial composition: Prebiotics are crucial for the regulation of physiological activities and can be used as carbon or energy sources for intestinal probiotics; however, they cannot be directly absorbed and utilized by the host^[38]. In brief, prebiotics promote the propagation and growth of probiotics, whose metabolites confer health benefits to the host^[42,43]. Some organic acids, for instance, are major metabolites generated by the metabolism of prebiotics by host microorganisms. The main organic acids generated are short-chain fatty acids (SCFAs) (*e.g.*, acetate, butyrate, and propionate), which directly decrease the colonic intraluminal pH; additionally, SCFAs can mediate multiple signaling pathways for maintaining gut homeostasis and immune system balance^[36,44,45]. Moreover, bile salt hydrolases, which are crucial hydrolytic enzymes, are also generated by enteric microorganisms. These hydrolases mediate transformation and/or metabolism of bile acids and possess resistance to the harsh acidic environment in the intestine, as well as confer host health benefits^[46,47]. Interestingly, a study showed that bacterial deconjugation of taurine from primary bile acids was enhanced after consumption of prebiotic inulin, which is consistent with the increased enzyme activity of bile salt hydrolases^[48].

Several studies evaluating the potential therapeutic effects of prebiotics on animal colitis models and IBD patients have demonstrated beneficial effects^[49-53]. HLA-B27

transgenic rats, as an effective rodent model of IBD, have been used to evaluate the potential therapeutic efficacy of inulin and FOS against intestinal inflammation. It was shown that both inulin and FOS decreased chronic intestinal inflammation by regulating the composition of gut microbiota, and increasing the abundance of probiotics *Bacteroides-Prevotella-Porphyromonas* and *Bifidobacteria*^[54]. Moreover, a recent experimental study of prebiotics in IBD models demonstrated that these agents play a strong beneficial role in relieving 2, 4, 6-trinitrobenzene sulfonic acid (TNBS)-induced colitis, which was correlated with increased abundance of probiotics (*Lactobacillus* and *Bifidobacterium*), as well as increased production of SCFAs^[55]. Interestingly, the preventive effects of prebiotic fiber against microbiota-mediated colonic mucus deterioration were revealed in another study; this effect may serve as a novel complementary mechanism by which prebiotics alleviate intestinal inflammation^[56]. However, recently, researchers have found that prebiotics, including fermentable fibers and inulin, can shift the normal microbiota composition to cause gut dysbiosis and overproduction of colonic butyrate, contradicting previous research outcomes^[57]. In comparison with animal studies of prebiotic applications, studies of prebiotics in IBD are very limited and remain controversial^[49]. In brief, based on the current results for prebiotic interventions, we cannot conclude that prebiotics ameliorate IBD symptoms^[58]. Further research is therefore necessary to confirm the potential of prebiotics to relieve IBD.

FMT

FMT is the transfer of fecal microorganisms from healthy donors to individuals with certain diseases, *via* technical approaches such as enemas, nasogastric or nasojejunal tubes, and oral capsules^[59]. FMT was first used to remedy pseudomembranous enterocolitis (PMC) in 1958, by Eiseman *et al.*^[60]. Later studies have suggested that PMC is caused by infection with the anaerobic bacterium *C. difficile*, which can induce gut dysbiosis^[61]. FMT has since been gradually extended from the preliminary development and testing phase to being used as an approved therapeutic modality for *C. difficile* infection (CDI) in the clinic, with a success rate of near 92%, thereby representing an effective treatment compared with broad-spectrum antibiotics^[62]. Subsequently, FMT has been used to treat IBD complicated by CDI, and finally extended to treat patients suffering only from IBD^[63]. As a treatment strategy for IBD, FMT has been proposed for over 25 years; however, it has only attracted research interest in the context of IBD in recent years^[64,65]. Several clinical investigations have demonstrated promising treatment outcomes for patients in the mild or moderate active period of the disease.

A systematic review in 2012 showed that, among 41 cases of FMT therapy in IBD patients, symptoms were relieved in 76% of patients, medication could be terminated in 76% of patients, and 63% of patients showed disease alleviation^[66]. However, subsequently, a larger-scale meta-analysis (307 adult patients) did not show as high a rate of effectiveness, reporting that FMT only mitigated the clinical symptoms of 36% of UC patients and 50.5% of CD patients^[67]. According to a small double-blind randomized trial, which was conducted to evaluate the safety and efficacy of FMT for UC patients, 41.2% of patients (7/17) achieved the primary endpoint compared with 25.0% of controls (5/20)^[68]. Similar results were also obtained in a recent multicenter, double-blind, randomized, placebo-controlled clinical trial, which demonstrated the validity of FMT in only 11 (27%) of 41 UC patients, with adverse reactions in 32 (78%) cases; however, most of the adverse events were self-limiting gastrointestinal complaints^[69]. Furthermore, based on 16S rDNA sequence analysis, FMT-induced clinical remission and endoscopic improvement are correlated with the regulation of intestinal microbiota in active UC^[69].

Data on FMT-induced CD alleviation are less abundant than in UC, and randomized controlled trials in CD are inadequate; only several small uncontrolled cohort studies have been carried out, producing conflicting results. A prospective open-label study showed that FMT from healthy donors to active CD individuals relieved symptoms in 58% (11/19) of CD patients, all of whom exhibited an increase in microbial diversity^[70]. In another uncontrolled study in 10 subjects to evaluate FMT, 3 of 10 CD patients responded to the intervention; however, 2 recipients showed serious adverse events, necessitating larger controlled trials to confirm the safety and efficacy of FMT^[71]. However, the results of a long-term multiple fresh FMT trial conducted to evaluate the maintenance effect of symptom relief in CD complicated by an intraabdominal inflammatory mass revealed that the clinical symptom alleviation rates were 48.0% (12/25), 32.0% (8/25), and 22.7% (5/22), respectively, at 6 mo, 12 mo, and 18 mo; fresh FMT was repeated every 3 mo^[72]. Furthermore, the long-term clinical effects of varied frequency of FMT for CD were explored: An interval of treatment of

less than 4 mo was shown to effectively maintain the clinical benefits obtained by the first FMT^[73]. However, the dynamic gut-microbiota shifts and molecular interactions between donors and recipients during FMT remain poorly understood. In addition, further studies are required to determine the optimal FMT treatment intensity and match the optimal donor-recipient types based on microbial profiles.

Herbal compounds and prescriptions

There are some safety concerns with the long-term use of conventional medications (e.g., anti-inflammatory, immunosuppressive, and biologic therapies), which has increased interest in traditional medicines for the treatment of IBD^[15]. Hence, an increasing number of researchers have shifted their attention to traditional medicine in order to identify potentially therapeutic compounds in Chinese herbal medicine and/or traditional prescriptions. So far, various potent compounds have been found, some of which exhibit the effects of relieving intestinal inflammation, at least in part by regulating the intestinal microbiota^[17]. However, paucity of data can actually reflect the therapeutic effect in human clinical trials^[74]. Numerous types of natural compounds are derived from herbs, including herbal polysaccharides, polyphenols, flavonoids, saponins, and alkaloids^[75]. Moreover, herbal polysaccharides and polyphenols, which are present in various Chinese herbs and mostly only absorbed in the colon, are yet to be included in the category of prebiotics^[76,77]. Herbs containing polysaccharides include some Chinese medicines such as *American ginseng* and *wolfberry*, which both show the ability to correct intestinal dysbiosis and mitigate intestinal inflammation in mice^[78,79]. Polyphenols in herbal medicines include anthocyanin, catechinic acid, ellagic acid, and gallic acid, which can be converted into bioactive metabolites by intestinal microorganisms. Therefore, modulation of the microbial community structure benefits the intestinal tract^[74].

Other non-prebiotic natural ingredients also exhibit the ability to attenuate intestinal inflammation in mice with colitis by selectively altering the gut microbiota; however, it has not been proven whether these compounds are involved in bacterial metabolism. Several natural alkaloids, such as berberine, palmatine, and evodiamine, have been shown to ameliorate experimental colitis in an IBD model by improving the relative abundance of gut microbiota, as well as increasing the abundance of *Bacteroidetes* and *Firmicutes* and reducing *Proteobacteria* abundance, thus maintaining the homeostasis of intestinal microbiota^[80-82]. A natural limonoid compound, obacunone (100 mg/kg/day *via* oral gavage in mice) abundantly distributed in *Phellodendron chinense* and *Tetradium ruticarpum*, exhibits a modulating effect on the disordered gut microbiota of IBD mice^[83]. Others, such as *Indigo naturalis* (200 mg/kg/day *via* oral gavage in mice) and *salvianolic acid* (8 mg/kg/day by tail vein injection in rats), also target the intestinal microbiota, with beneficial effects on gut health^[84,85]. Moreover, recent studies have also demonstrated the efficiency of several traditional Chinese prescriptions: As a traditional compound, Bawei Xileisan (200 or 400 mg/kg/day *via* oral gavage) consists of 8 Chinese medicines, includes watermelonfrost, calcite, cowgallstone, pearl powder, borax, *Dryobalanops aromatica* Gaertn. f., ammonium chloride, and *Indigo naturalis*, and has been shown to relieve colitis in the mouse model of UC mainly by restoring Th17/Treg imbalance and improving *Lactobacillus* abundance^[86]. Rhubarb Peony decoction is another Chinese prescription that increasing *Butyricicoccus pullicaecorum* abundance and SCFA levels, thus alleviating pathological changes in colitis mice^[87]. Recently, Pyungwi-san (669.1 mg/kg/day *via* oral gavage) was found to protect against DSS and *C. difficile*-induced colitis mice, and the mechanism was related to restoration of a balance in gut microbial communities^[88].

POTENTIAL THERAPEUTIC MECHANISMS BY WHICH INTESTINAL MICROBIOTA ARE TARGETED

The above-mentioned emerging treatment strategies targeting intestinal microbiota, which share a common direct initiation mechanism, show varying efficacy in terms of regulating dysbiosis (including the inhibition of pathogenic microorganisms and promoting the entire gut microbiota community). Furthermore, gut dysbiosis is often concomitant with the reduction in beneficial metabolites, impairment of intestinal barrier function, and imbalance of immunity homeostasis^[89]. Therefore, potential therapeutic mechanisms by which intestinal microbiota are targeted may involve regulating microbial metabolism, enhancing the epithelial barrier, and maintaining intestinal immune homeostasis.

Regulating microbial metabolism

The hallmark of dysbiosis is the reduction in the abundance of commensals and the increase in pathogenic microbes. Commensal intestinal microbes play a crucial biological role in the host by producing bioactive metabolites such as SCFAs, trimethylamine, trimethylamine *N*-oxide, and tryptophan metabolites^[90]. Among them, SCFAs represent a significant proportion of microbial metabolites, whose peak concentrations can reach 130 mM in the proximal colon^[91]. The biosynthetic pathways of SCFAs were briefly reviewed by Zhang *et al.*^[90]. Acetate, propionate, and butyrate are the most abundant SCFAs, and are used as energy substrates for absorption and utilization by the intestinal epithelium, promoting intestinal health and reducing inflammation^[92]. Studies have found that butyrate-producing bacteria, *Roseburia hominis* and *F. prausnitzii* belonging to *Firmicutes*, are dramatically decreased in UC patients compared with levels in healthy individuals^[93]. Interestingly, the effective utilization of probiotics and prebiotics increases the generation of SCFAs by promoting the proliferation of commensal bacteria, mainly SCFA-producing bacteria (e.g., *Ruminococcus* and *Faecalibacterium*)^[94,95]. Furthermore, FMT also exhibits the biofunctionality of enhancing SCFA production^[96].

As an essential amino acid, tryptophan is found naturally in many foods such as fish, eggs, and red meat. Altered levels of tryptophan and tryptophan metabolites have been revealed in IBD patients by metabolomics analysis, and the expression of the aryl hydrocarbon receptor (AhR) in inflammatory intestinal tissues is reduced compared with that in healthy individuals^[91,97]. Moreover, the ability of several microorganisms to metabolize tryptophan to serotonin (5-hydroxytryptamine), kynurenine (Kyn), indole and indole derivatives (e.g., indole-3-aldehyde; I3A) has been reported; the first-discovered tryptophan-degrading bacteria are *Escherichia coli* and *Vibrio cholera*^[98,99]. Both indole and I3A are ligands of the AhR; these bind AhR and thus regulate Th17/Treg immune homeostasis, maintaining the balance of mucosal reactivity^[100]. Several probiotics have been shown to affect the levels of tryptophan metabolites. For example, *Lactobacillus* present in the intestine, which spontaneously generates AhR agonists and protect against colitis with dysbiosis in gene-deficient mice (Card^{-/-}), has potential therapeutic effects involving the regulation of tryptophan metabolism^[101]. Moreover, as an important probiotic, *Lactobacillus reuteri* strains can reduce intestinal inflammation by inducing tryptophan-derived indole production, thus activating the AhR and promoting gut intraepithelial Treg cell differentiation^[102]. Two natural substances, patchouli alcohol and palmatine, derived from *Pogostemon cablin* and *Golden thread*, respectively, have been shown to relieve DSS-induced experimental colitis, at least partly by suppressing tryptophan catabolism^[81,103]. However, the relationship between microbial metabolism and intestinal health remains poorly understood, and the construction of microbial metabolism regulatory networks may be a promising research avenue to help clarify the orchestrated therapeutic mechanisms by which intestinal microbiota are targeted.

Protecting and enhancing the epithelial barrier

The integrity of the intestinal epithelial barrier is a prerequisite for intestinal mucosal immune homeostasis; the mucosa is an indispensable protective layer against chemical and pathogenic challenges from the colonic lumen^[104]. Studies also describe the therapeutic potential of protecting and enhancing the epithelial barrier in IBD treatment^[105]. Several probiotic strains possess the ability to protect or enhance the epithelial barrier, as shown by several *in vitro* studies, animal IBD models, and clinical trials^[106-108]. An earlier *in vitro* study found that probiotic strains, including those of *Streptococcus* and *Lactobacillus*, protected against intestinal epithelial barrier lesions caused by enteroinvasive *Escherichia coli*^[109]. Subsequent studies have shown that probiotics compete with pathogenic bacteria for adherence to mucosal sites, reflecting the anti-adherence function of probiotics and therefore supporting the mechanism of epithelial barrier protection by probiotics^[110,111]. For example, *Lactobacillus plantarum*, a well-known probiotic, can competitively prevent enteropathogenic *Escherichia coli* and mannose adhesion-dependent enteric pathogens (e.g., *S. typhimurium*) from adhering to intestinal epithelial cells^[112,113]. In addition to these direct anti-adherence functions of probiotics, other mechanisms involving the suppression of toxin secretion by pathogenic microorganisms may also protect the intestinal barrier. *Bifidobacterium breve* strain Yakult, for instance, was found to inhibit the production of Shiga toxin derived from *Escherichia coli* O157:H7 *in vitro* as well as in a lethal mouse *Escherichia coli* infection model^[114]. Interestingly, a more precise probiotic mechanism has been reported in that the probiotic yeast protease, secreted by *Saccharomyces boulardii*, degrades toxin A produced by *C. difficile*^[115].

In addition to the indirect protective effect on the epithelial barrier, probiotics can enhance intestinal epithelial barrier function directly^[116]. It has been widely confirmed that probiotics can strengthen the intestinal barrier by increasing the expression levels of TJ proteins both *in vitro* and *in vivo*^[117]. The *Lactobacillus rhamnosus* GG-derived protein, p40, promotes intestinal epithelial proliferation, differentiation and the formation of TJ proteins^[118]. In addition, the expression levels of intestinal TJ proteins, such as claudin, occludin, and zonula occludens 1 (ZO-1) were significantly increased in newborn piglets after the administration of *Lactobacillus reuteri*^[119]. Moreover, the ability of *Lactobacillus plantarum* to recruit occludins and ZO-1 to the TJ region has been reported in a clinical trial^[117]. Furthermore, probiotic *Bifidobacteria* show similar effects to *Lactobacillus*, in terms of increased expression of ZO-1 and occludin by promoting the activation of extracellular signal regulated kinases and the p38 signaling pathway in human epithelial cells^[120]. In addition, a recent study revealed that TNBS-induced gut barrier dysfunction was improved noticeably after *Bifidobacterium longum* treatment owing to suppression of high mobility group box 1 protein release^[106]. Except for the single probiotic, several probiotic mixtures present a similar efficiency. Bifico, for example, which is a probiotic mixture comprising *Bifidobacterium*, *Lactobacillus acidophilus*, and *Enterococcus*, was shown to upregulate the expression of TJs in IL10^{-/-}/TNBS-induced models^[121]. However, similar evidence in clinical settings is scarce, and further study is warranted (Figure 2).

CLINICAL APPLICATIONS IN IBD TREATMENT

Compared with IBD, probiotics and prebiotics have been extensively applied to treat clinical gastrointestinal disease. Mild-to-moderate IBD or IBD accompanied by *C. difficile* infection are the main types of IBD that fit the scope of treatment with pro/prebiotics^[23]. The British Society of Gastroenterology consensus guidelines published in 2019 point out that pre/probiotics, symbiotics, FMT, and herbal treatments are all complementary and alternative therapies for IBD in adults^[18]. Although there is insufficient evidence to conclude that probiotic therapy induces remission of IBD, it may improve symptoms, at least to some extent, in mild-to-moderate UC^[122]. A subsequent study revealed that the evidence for maintaining remission is insufficient, and the only data demonstrating benefits are from patients with UC^[123,124]. The effects of probiotics on CD are controversial: A nonblind clinical trial demonstrated the safety and efficacy of probiotics to treat CD; however, a meta-analysis indicated that CD symptoms cannot be mitigated by probiotic treatment^[125,126]. The evidence for prebiotics is relatively scarce compared with that for probiotics, and the data in humans remain ambiguous. As a prebiotic, lactulose has shown certain benefits in UC and CD patients when administered at a daily dosage of 20 g^[127]. In comparison, the other two prebiotics, inulin and FOS, have shown mixed results in terms of clinical outcomes, demonstrating bioavailability in one small open-label study but no effects in a much larger study^[128,129]. Moreover, the use of probiotics and prebiotics in the treatment of IBD usually in conjunction with conventional medications provides limited evidence.

Four randomized placebo-controlled trials have been conducted on FMT to date; among these, three have shown a significant symptom reduction compared with placebo^[18]. An open-label study revealed that FMT is more applicable to UC than CD patients^[130]. Nevertheless, unified standards for the route and frequency of FMT administration in published trials are not available, which may be a potential reason for the discrepancies between them^[131]. Establishment of the optimal route and frequency of FMT administration, therefore, may provide a strong theoretical foundation and practical guidance for the clinical application of FMT. Quality control of donor feces is also critical for clinical application and to increase the stability and security of FMT^[132]. Recently, the U.S. Food and Drug Administration notified the potential risk of serious or life-threatening infections with the use of fecal microbiota for FMT, and claimed that bacterial infections are caused by multi-drug resistant organisms^[133]. Thus, the potential risk of FMT reminds researchers again to focus more on how to increase the stability and security of FMT. The proposed implementation of stool banks is a promising step toward the establishment of unified standards for donor feces^[134]. The Netherlands Donor Feces Bank was the first stool bank, established in 2015, aiming to provide a standard product for treating recurrent CDI in the Netherlands^[132]. Subsequently, FMT experts held an international consensus conference on stool banking, which confirmed the feasibility and maneuverability of stool banking to accelerate FMT application in clinical settings^[135]. In general, it is a

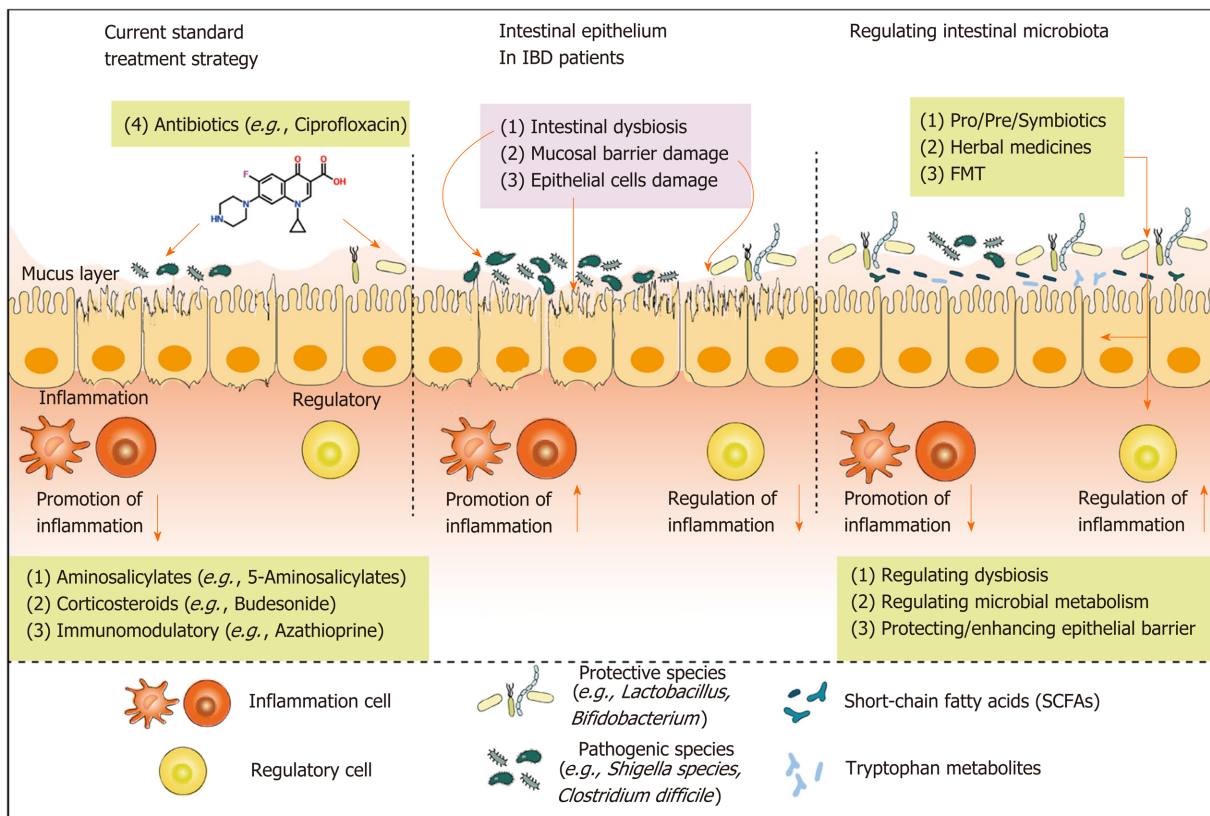


Figure 2 Primary mechanisms of standard treatment strategy and regulating intestinal microbiota strategy for inflammatory bowel disease. Current standard therapeutic medications for inflammatory bowel disease (IBD) are antibiotics (e.g., ciprofloxacin), aminosalicylates (e.g., 5-aminosalicylates), corticosteroids (e.g., budesonide) and immunomodulatory agents (e.g., azathioprine), and the mechanism mainly involves inhibiting the development of inflammation in the intestine. Intestinal dysbiosis is often found in IBD patients, which is manifested in higher abundance of pathogenic species (e.g., *Shigella species* and *C. difficile*) and less abundance of protective species (e.g., *Lactobacillus* and *Bifidobacterium*). However, interventions targeting intestinal microbiota, such as probiotics, prebiotics, symbiotics, herbal medicines and fecal bacteria transplantation exert therapeutic action primarily through the mechanism of correcting dysbiosis. Furthermore, the treatment strategy of regulating intestinal microbiota are also involved in regulating microbial metabolisms (e.g., short-chain fatty acids and tryptophan metabolites), and protecting/enhancing the intestinal epithelial barrier. IBD: Inflammatory bowel disease; FMT: Fecal bacteria transplantation.

solid foundation for the extensive exploration and promotion of FMT that ensure recipients receive security, reliable, timely and equitable donor feces.

Although some herbal medicines have already been used in clinical settings as complementary and alternative medicine for IBD, their underlying pharmacologic modes of action remain obscure^[136]. The mechanisms by which herbal compounds and prescriptions target intestinal microbiota have been described in experimental IBD models. These findings may represent only the tip of the iceberg in regard to the potential therapeutic mechanisms of herbal therapies.

CONCLUSION

Microbe-based therapies for IBD discussed in this review may be separated into two categories, namely: Those that directly target microbiota (probiotics and FMT) and those whose mechanisms involve indirect regulation (prebiotics and herbal medicines). IBD is a complex disease that correlates with immune, microbial, and environmental factors. Current treatment methods suffer limitations and offer low effectiveness with the rapid rise in IBD incidence. However, the emergence of microbe-based therapies affords an avenue in the pursuit of more effective and personalized treatment plans for IBD patients. Oka A and Sartor RB proposed that concomitant companion diagnostic tests should be carried out to profile an individual's microbiota for guiding optimal personalized microbial therapies^[137]. It is well known that the development of new therapies often accompanies the innovation of new methods and techniques. Therefore, the development and improvement of microbe-based therapies require multi-disciplinary approaches (such as genomics, microbiology, and

metabolomics), to obtain a deeper and more comprehensive understanding of the co-regulatory networks between microbiota, bacterial metabolites, and host immunity.

Probiotic strains that are known and applied, to date, have been derived from bacteria or fungi, but not viruses^[24,138]. For example, the *Bifidobacterium* and *Lactobacillus* genera have been commercialized worldwide, and next-generation probiotics (*Faecalibacterium prausnitzii*, *Akkermansia muciniphila*, and *Eubacterium hallii*) are emerging^[138]. However, high-throughput sequencing shows that the dominant viruses that inhabit the intestines are *bacteriophages* (e.g., *prophages*), which can shape and influence the bacterial community structure by parasitizing or lysing bacterial cells^[139,140]. Therefore, future studies of probiotics should endeavor to focus on intestinal bacteriophages in order to elucidate the mechanisms underlying the relationships between bacteriophages and bacteria, with a view to identifying novel virus-based probiotics. Furthermore, the use of probiotics to find effective small-molecule chemicals (metabolites) or structural proteins may represent additional promising research directions.

Complementary therapies targeting the intestinal microbiota are indistinguishable, which do not follow the individual therapeutic scheme. Nevertheless, the intestinal microbial composition in different patients are highly individualized. Hence, it is necessary to screen the microflora and conduct follow-up investigations for different IBD patients in order to monitor individual differences in microbiota and design personalized microbiota-based therapies in order to enhance the specificity and selectivity of the therapeutic strategy targeting intestinal microbiota.

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