The emerging microbiome-based approaches to IBD therapy:From SCFAs to urolithin A

by Mohammad Rudiansyah

REVIEW ARTICLE

Journal of Digestive Diseases   **WILEY**

The emerging microbiome-based approaches to IBD therapy: From SCFAs to urolithin A

Mohammad Rudiansyah[1] | Saade Abdalkareem Jasim[2] | Bakhadir S. Azizov[3] | Vadim Samusenkov[4] | Walid Kamal Abdelbasset[5] | Ghulam Yasin[6] | Hawraa Jabbar Mohammad[7] | Mohammed Abed Jawad[8] | Trias Mahmudiono[9] | Seyed Reza Hosseini-Fard[10] | Rasoul Mirzaei[11] | Sajad Karampoor[12]

[1]Division of Nephrology & Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas Lambung Mangkurat, Ulin Hospital, Banjarmasin, Indonesia

[2]Al-Maarif University College Medical Laboratory Techniques Department Al-Anbar-Ramadi, Ramadi, Iraq

[3]Department of Therapeutic Disciplines No.1, Tashkent State Dental Institute, Tashkent, Uzbekistan

[4]Sechenov First Moscow State Medical University, Moscow, Russia

[5]Department of Health and Rehabilitation Sciences, College of Applied Medical Sciences, Prince Sattam bin Abdulaziz University, Al Kharj, Saudi Arabia

[6]Department of Botany University of Bahauddin Zakariya University, Multan, Pakistan

[7]Al-Manara College For Medical Sciences, Maysan, Iraq

[8]Al-Nisour University College, Baghdad, Iraq

[9]Department of Nutrition Faculty of Public Health Universitas, Airlangga, Indonesia

[10]Department of Biochemistry, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[11]Venom and Biotherapeutics Molecules Lab, Medical Biotechnology Department, Biotechnology Research Center, Pasteur Institute of Iran, Tehran, Iran

[12]Gastrointestinal and Liver Diseases Research Center, Iran University of Medical Sciences, Tehran, Iran

Correspondence

Rasoul Mirzaei, Venom and Biotherapeutics Moleculs Lab, Medical Biotechnology Department, Biotechnology Reserch Center, Pasteure Institute of Iran, Tehran, Iran.
Email: rasul.micro92@gmail.com

Sajad Karampoor, Gastrointestinal and Liver Diseases Research Center, Iran University of Medical Sciences, Tehran Hemat Highway next to Milad Tower, 14535, Tehran, Iran.
Email: sajadkarampour1987@gmail.com

Inflammatory bowel disease (IBD) is a group of chronic gastrointestinal inflammatory conditions which can be life-threatening, affecting both children and adults. Crohn's disease and ulcerative colitis are the two main forms of IBD. The pathogenesis of IBD is complex and involves genetic background, environmental factors, alteration in gut microbiota, aberrant immune responses (innate and adaptive), and their interactions, all of which provide clues to the identification of innovative diagnostic or prognostic biomarkers and the development of novel treatments. Gut microbiota provide significant benefits to its host, most notably via maintaining immunological homeostasis. Furthermore, changes in gut microbial populations may promote immunological dysregulation, resulting in autoimmune diseases, including IBD. Investigating the interaction between gut microbiota and immune system of the host may lead to a better understanding of the pathophysiology of IBD as well as the development of innovative immune- or microbe-based therapeutics. In this review we summarized the most recent findings on innovative therapeutics for IBD, including microbiome-based therapies such as fecal microbiota transplantation, probiotics, live biotherapeutic products, short-chain fatty acids, bile acids, and urolithin A.

1 | INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a group of chronic inflammatory conditions of the gastrointestinal tract that affects 6.8 million individuals worldwide.[1] The pathophysiology of IBD is multifaceted.[2] Aberrant immune response due to immune dysregulation leads to chronic inflammation; hence, most studies on IBD pathophysiology have been directed toward immune aberrations.[2] Cytokines and cytokine signaling, such as tumor necrosis factor (TNF) and Janus kinase (JAK), play essential roles in the pathophysiology of IBD.[3] Targeting these crucial cytokines, such as TNF, has received much more attention in IBD treatment for patients who do not respond to corticosteroids or immunosuppressants.[3] Small-molecule (non-immunogenic oral) therapeutics, including JAK inhibitors, have illustrated efficiency in the initial-phase clinical trials, leading to authorization of tofacitinib to manage cases with moderate-to-severe UC.[4] Substantial progress has been made in recent decades in the investigationg of the development of the disease. According to previous studies, the pathogenesis of IBD is linked to genetic vulnerability of the host, altered gut microbiota, environmental factors, and immunological disorders.[5,6] Among the environmental cues, it has been shown that gut microbial dysbiosis plays a critical role in the pathogenesis of IBD.[7] The host in healthy status benefits from gut microbiota, which includes production of short-chain fatty acids (SCFAs) and amino acids, metabolism of undigested carbohydrates, and immune system activation.[7] Compared to healthy individuals, the composition and diversity of gut microbiota significantly change in cases with IBD.[7]

Ruminococcus bromii and *Faecalibacterium prausnitzii* are two of the most critical bacteria in generating butyrate via undigested dietary fiber, which is a raw material for producing numerous SCFAs in the gut.[8,9] SCFAs can be found in both the small and large intestines, including formic acid, butyrate, valeric acid, acetate, and propionate (mainly found in small and large intestines).[8,9] Butyrate can be found in the colon and cecum.[10] Generally, these SCFAs improve the intestinal barrier, provide adequate energy to gut epithelial cells, and decrease inflammation. G-protein coupled receptor 43 (GPR43) plays a role in promoting the effect of SCFAs on the synthesis of interleukin (IL)-10 by T helper 1 (Th1) cells that are specific for microbial antigens.[11] By boosting Th1 cells to produce IL-10, SCFAs reduced the pathogenicity of gut microbiota antigen-specific Gpr43$^{-/-}$ CBir1 transgenic Th1 cells in the induction of intestinal inflammation.[11] Notably, SCFAs promote IL-10 synthesis by human T cells, showing their unique therapeutic benefits in managing IBD.[11] A disturbed gut microbiota in IBD reduces butyrate synthesis compared with healthy controls.[12] Some butyrate-producing bacteria produce significantly less butyrate in UC patients, resulted in a decline in SCFAs in the gut lumen.[13] Oral butyrate might boost the effectiveness of oral mesalazine in treating active UC, and IBD patients on a SCFAs-rich diet have reported improved colitis as well.[8,14]

Urolithin A (UroA), a significant microbial metabolite generated from polyphenolic chemicals in berries and pomegranate fruits, and its synthetic structural analogue UAS03 have recently been found to protect against IBD.[15] In addition, Sinha et al[16] indicated that some bacteria could convert primary bile acids (PBAs) to secondary bile acids (SBAs), which have a protective function toward the progression of IBD. Fecal microbiota transplantation (FMT) is a potential treatment strategy for IBD.[17] Utilizing live biotherapeutic products (LBPs), including single strains of beneficial probiotic bacteria or consortiums, is becoming a feasible therapeutic strategy for treating inflammatory-mediated disorders like IBD.[18] Numerous studies have highlighted the potential impact of probiotic bacteria on gut microbiome and production of metabolites, notably SCFAs.[19] Nevertheless, the persistence of LBPs in the gut varies because many beneficial bacteria lose their ability to resist inflammatory and oxidative damage related to IBD.[18] In this review we described and discussed the latest data concerning novel approaches to IBD treatment, including FMT, probiotics, LBPs, bile acids (BAs), UA, and SCFAs.

2 | IMMUNOPATHOGENESIS OF IBD

According to prevailing opinion, CD and UC have terminally differentiated immunophenotypes.[20] The IL-12/interferon (IFN)-γ/TNF cytokine axis has long been thought to mediate CD as a characteristic Th1 condition.[20] Since anti-TNF and anti-IL-12 agents have been used to treat CD, this notion has been reinforced.[20] The concept that UC exhibits an uncommon T helper 2 (Th2) cell profile of immunologic response, on the other hand, has never been confirmed. Instead, it is a theory of "exclusion" that helps highlight and explain its distinctions from CD.[20] As a consequence of the recent breakthroughs in the research on the etiology of intestinal tissue damage, this pathophysiological hypothesis for IBD is progressively improving (Figure 1).

Discovery of the third kind of immune response (effector), the pathway of IL-23/IL-17, is a significant advance.[21] IL-23 is a heterodimeric cytokine that shares its p40 subunit with IL-12 but binds it with the p19 subunit rather than the p35 subunit, which activates this pathway. A colony of T cells (T helper 17 [Th17] cells) are stimulated by IL-23, generating factors including IL-17, IL-6, and TNF-α.[22] The toxic effects of these cells have been reported in many diseases.[21]

Recent studies have linked the Th17 pathway to chronic intestinal inflammation. Yen et al[23] demonstrated that IL-23, not IL-12, was required to establish colonic inflammation in the colitis model using an IL-10-knockout mouse. The injection of synthetic IL-23 increased the severity of colitis elicited in immunologically naïve recombinase activating gene (*Rag*)-deficient mice by transplanting IL-10$^+$CD4$^+$ cells
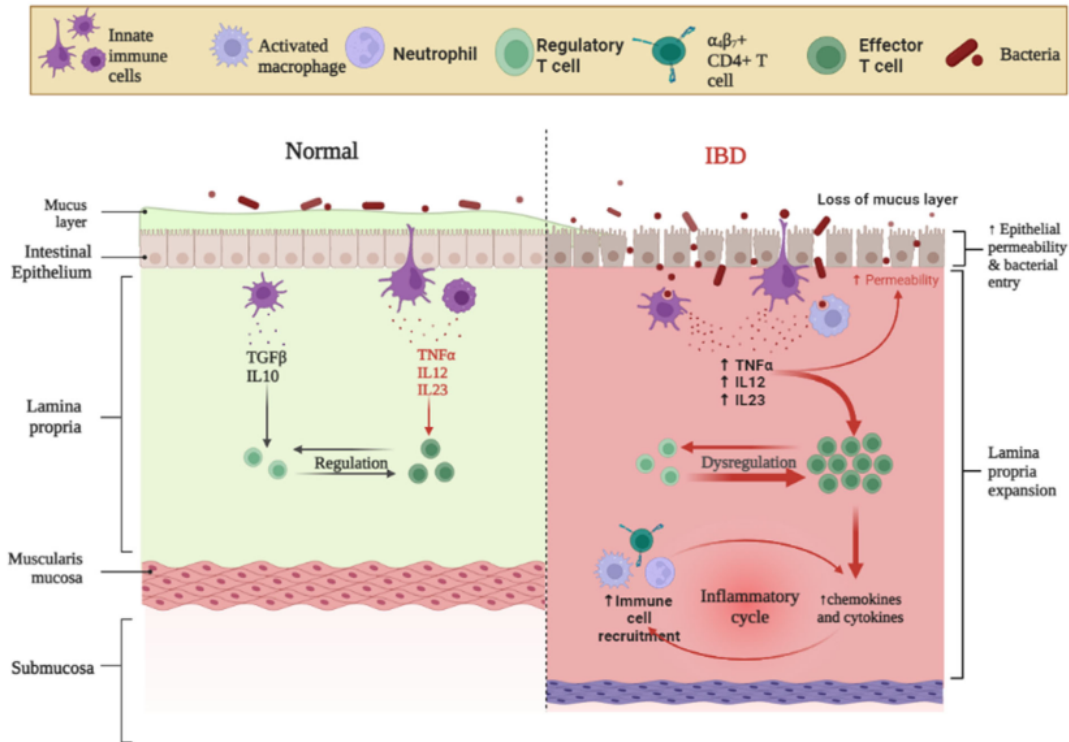
FIGURE 1 Schematic illustration of immunopathogenesis of inflammatory bowel disease (IBD). The fundamental operator of IBD is a dysfunctional mucosal immune reaction, presenting as modified innate immunity, activated effector T cells, enhanced recruitment of B cells and antibody production, and elevated proinflammatory markers, among other factors. This figure depicts the immune cells implicated in IBD pathophysiology and cytokines formed by various cell subsets in the influenced mucosa. Chronic intestinal inflammation is caused by inappropriate activation and maintenance of inflammatory responses triggered by cytokines and a lack of control over these responses due to impaired regulatory mechanisms and anti-inflammatory cytokines such as interleukin (IL)-10 and transforming growth factor (TGF)-β. Abbreviation: TNF, tumor necrosis factor

in immunologically naïve *Rag*-deficient animals. The proinflammatory T cell subset (memory) was induced by IL-23, generating IL-17 and IL-6, both of which were associated with tissue injury.[24] Another model of colitis was established by T cells (induced by *Helicobacter hepaticus*),[25] showing similar results in previous research. In this model, the inflamed cecum overexpresses IL-23 and IL-17, and blocking IL-23p19 with antibodies decreased the production of the proinflammatory agent. Transplantation of CD4+CD45RBhi cells into *Rag*-deficient animals (p35Rag−/−) led to severe colitis, although recipients (p19Rag−/− or p40Rag−/−) were protected from colitis. According to these findings, progression of intestinal inflammation in this IBD model requires IL-23 but not IL-12. The implications of activating the Th17 pathway are being studied. There are data showing that IL-17 affects the innate immunity in trinitrobenzene sulfonic acid (TNBS)-induced colitis by increasing the augmentation of macrophage inflammatory protein 2 and promoting the aggregation of neutrophils in the injured tissues.[26] IL-17 generating CD4+ T cells might interplay with colonic subepithelial myofibroblasts, modifying their production of cytokines and chemokines, resulted in augmentation of proinflammatory reactions and aggravation of tissue injury.[27]

Most animal models of colitis have shown that the Th17 pathway is crucial for advancing inflammatory response. Furthermore, IL-23 and IL-17 expressions in the inflammatory area of patients with CD are elevated.[28,29] These findings increase the probability that mouse immunologic processes are also relevant in human beings. It also seems that a positive impact of anti-IL-12 p40 antibodies on CD was accomplished via inhibiting IL-23 signaling instead of IL-12 signaling.[30] The finding that patients given anti-p40 antibodies had lower IL-17 and IL-6 synthesis support this theory.[31] Remarkably, a recent genome-wide association analysis (GWAS) has revealed a powerful association between CD and a component of IL-23 receptor (IL23R) that is produced by a gene located on chromosome 1p31.[32] Replication investigations verified *IL23R* associations in independent cohorts of CD or UC, showing a probable pathogenic involvement of IL-23 in IBD.[32]

In addition to the Th17 pathway, there is evidence that additional courses, especially those mediated with cytokines, play crucial roles throughout inflammatory process in the mucosa. TNF-like cytokine 1A (TL1A), also known as TNF superfamily member 15 (TNFSF15), is a member of the TNF family (new TNF-like cytokine) that can bind to

receptors with conflicting activities, that is, the functional receptor death-domain receptor 3 (DR3) and the inhibitory receptor decoy receptor 3 (DcR3), which competes with DR3 for TL1A attachment.[33] Recent research on SAMP1/YitFc and TNF$^{\Delta ARE}$ mice (models of CD), both of which develop ileitis spontaneously, suggests that TL1A signaling through DR3 may play a role in the pathophysiology of chronic inflammation in the gastrointestinal system. During chronic ileitis, expression of the mRNA that encodes TL1A and DR3 dramatically increases. TL1A is produced predominantly on dendritic cells (DCs) resident in the mucosal area and operates primarily on memory CD4$^+$ T cells to supply costimulatory signals for replication and production of IFN-γ. The activities of TL1A (expressed on mucosal DCs) are unaffected by IL-18.[34] Since both molecules are overexpressed in individuals with active CD and UC, interplays between TL1A (expressed on antigen-presenting cells) and DR3 (expressed on activated lymphocytes) may be particularly important for IBD pathophysiology.[35,36] Furthermore, *TNFSF15* gene single-nucleotide polymorphism (SNP) increases the risk of CD.[37] *TNFSF15* was the first gene that was found to be related to CD susceptibility worldwide, which is noteworthy given that the association is independent of ethnic origin.

3 | GUT MICROBIOTA AND IBD

Humans have a symbiotic relationship with the microbiota in the gastrointestinal tract, which contains about 100 trillion microorganisms, comprising 1000 kinds of microorganisms and 1 million related genes.[38,39] Technological advances in genetic investigation have revealed that the disruption of the human–enteric symbiotic ecosystem, known as dysbiosis, is significantly associated with the emergence of new disease groups, notably IBD, in developed countries.[7] Even though microbiota may be as basic as parasites that attach to human host nutrients or "friendly" microbes that colonize the gut to promote fermentation, westernized lifestyle has made it increasingly challenging to house these "good" microbes in the intestine.[7] This lifestyle includes a high-fat, low-fiber diet, synthetic milk, inappropriate use of antibiotics, cesarean section, improved hygiene, and stress, all of which can lead to dysbiosis.[40] Dietary fiber is a key nutrient for microbiota, and a reduction in dietary fiber consumption is thought to be the major cause of dysbiosis.[7]

Microbiota, along with genetic makeup and immunological variables, play a significant role in the pathogenesis of IBD.[41] Current studies have evaluated gut microbiota using high-resolution using next-generation sequencing (NGS) technology and found lower heterogeneity of gut microbiota in patients with IBD.[41] Frank et al[42] demonstrated that in IBD patients the abundances of bacteria belonging to the phyla Firmicutes and Bacteroidetes were decreased. In contrast, those belonging to the phyla Actinobacteria and Proteobacteria were increased. In addition, the phylum Firmicutes, and specific members of Clostridium cluster IV, *Faecalibacterium prausnitzii* (*F. prausnitzii*), are decreased in the feces of CD patients, according to Sokol et al' studies.[43,44] Subsequent notable investigations have consistently indicated 17 Clostridia strains

from clusters IV, XIVa and XVIII activates regulatory T cells (Tregs) in the gut.[45,46]

Despite the immunosuppressive effects of some bacteria, no single pathogen has been shown to induce damage in IBD patients. *Mycobacterium avium* subspecies *paratuberculosis*, for instance, has long been accused of having a pathogenic influence on CD, that is, similar to granuloma-forming mycobacterium infectious illnesses.[47] In a 2-year clinical trial, antitubercular medication including with clarithromycin, rifabutin, and clofazimine given to CD patients showed no efficacy.[48] The link between CD and other bacterial taxa, including Listeria and Mycoplasma, was studied.[49,50] Recent research has uncovered a possible link between "pathogenic" bacteria and the breakdown of intestinal homeostasis. The bacterium adherent-invasive *Escherichia coli* (AIEC) has been identified from ileal biopsy specimens of the subjects with CD. AIEC causes disease by adherence to and attacking intestinal epithelial cells.[51] AIEC also increases macrophages and induces macrophage release of TNF-α.[51] In UC patients, *Fusobacterium varium* has been shown to adhere to swollen mucosa and enter the inflamed mucosa.[52] Aside from emphasizing these specific bacteria, changes in the composition of gut microbiota have been linked to the etiology of IBD or prediction of disease progression. In CD patients, *F. prausnitzii* is implicated in developing postoperative relapse.[44] It has also been proven that 5-aminosalicylic acid (5-ASA) intolerance is related to an increased risk of severe clinical consequences and dysbiosis.[53] It is notably that computational methods of gut microbiota enable predicting the efficiency of a specific biologic therapy on UC.[54] In summary, gut homeostasis is regulated by a varied microbiota containing possibly "good" microbes, whereas other particular bacteria may be related to IBD development. Nevertheless, it is debatable whether IBD-associated dysbiosis in gut microbiota is a driver or a result of gut inflammation.

4 | RECENT ADVANCES BASED ON MICROBIOME IN IBD TREATMENT

In addition to minimizing disease recurrence, traditional therapy with pharmacological strategies employing conventional drugs, including aminosalicylates, corticosteroids, thiopurines, folic acid antagonists, or biological medicines, are utilized to manage inflammation.[24,55] On the other hand, these methods are not completely effective, and patients may develop resistance or become intolerant to the drugs. Interventions to modify the microbiome have been proposed as one of the most promising approaches for treating immune-mediated disorders like IBD in this setting.[56] This is relevant because current research shows that traditional therapies, especially when combined with specific diet, fail to entirely preserve the normal microbiota in IBD patients.[57]

Gut microbiota has been significantly involved in health and disease pathophysiology in recent decades.[58] Small molecules generated as intermediate and final products of microbial metabolism are one crucial way gut microbiota communicate with the host.[58] The metabolites may be derived from bacterial metabolism of dietary sources,

manipulating host molecules including BAs, or directly from bacteria.[59] Microbial metabolite signals control immune development, homeostasis, metabolism, and mucosal integrity preservation of the host.[58] Variations in the microbiota composition and function have been identified in several IBD experiments.[58] SCFAs are cardiac representations of advantageous metabolites.[60] The most essential and plentiful SCFAs produced by intestinal microbiota are acetate, propionate, and butyrate.[60] Various degrees of decreased fecal SCFA levels in patients with IBD have been reported.[61–64] UroA, a microbial metabolite generated from polyphenolics in berries and pomegranate fruits, has antiinflammatory, antioxidant, and antiaging properties.[15] The function of UroA (derived from ellagic acid [EA] by intestinal bacteria) and its artificial forms UAS03 and BA in the pathophysiology of IBD has been identified.

Increasing studies have focuses on the interplay routes formed between prokaryotic and eukaryotic cells in both diseased and healthy states and the dynamic and advantageous equilibrium between gut microbiota and the host.[65] Numerous pleiotropic substances are synthesized by microorganisms that colonize the human gastrointestinal tract. These compounds influence the development and homeostasis of the immunity, energy, and metabolism of the host, as well as the preservation of epithelial barrier activity, which protects against infection.[66] Compared to commonly reared controls, germ-free (GF) animals exhibit substantial variations in concentration of the metabolites in various biological tissues, such as the gut. As a result, GF animals require a higher caloric intake to preserve the same body weight, and they are more susceptible to vitamin deficiencies, necessitating the use of dietary supplements.[66] Dysbiosis associated with IBD may modify the metabolic profile of the bacteria, which in turn influences the homeostasis of the host organism, with significant variations in the concentrations of metabolites with immunomodulatory characteristics, such as SCFAs, BAs, and tryptophan metabolites, which predisposes the host to mucosal inflammation.[60] The production of beneficial bacterial metabolites may be impaired in IBD patients, which negatively affects gut–brain interaction.[67] Several microbiota-based therapies, including metabolites (SCFAs, UroA, and BAs), FMT, probiotics, LBPs, and bacteriophages in IBD are summarized in Table 1.

4.1 | SCFAs and IBD

SCFAs, which are primary metabolites generated in the colon via microbial fermentation of nutrients and dietary fibers, are thought to play a significant role in immunomodulation.[68] Bacterial species that live on nondigestible dietary fibers and create metabolites that positively impact the mucosal surface, such as SCFAs (primarily acetate, propionate, and butyrate), appear to be highly significant.[68] By acting as an anti-inflammatory agent and a critical energy source for colonocytes, butyrate is essential for maintaining healthy epithelial tissue.[69,70] SCFAs can influence cell growth, development, and gene expression directly or indirectly at the cellular level.[68] Simple diffusion

may be used to absorb them, but specialized transporters including the monocarboxylate transporter 1 (MCT1) and the sodium-coupled monocarboxylate transporter 1 (SMCT1) significantly improve absorption via intestinal epithelial cells. In addition, SCFAs activate anti-inflammatory pathways by binding to G-protein-coupled receptors (GPCRs), including GPR41, GPR109A, and GPR43.[68]

SCFAs have a role in the regulation of CD4$^+$T cell development into Th17 and Tregs.[71] The transcription factor known as retinoic acid-related orphan receptor γt (RORγt) prompts the Th17 cells to manufacture massive amounts of proinflammatory cytokine known as IL-17.[72] Forkhead box P3 (Foxp3) is a transcription factor that regulates the development of Tregs, which mainly express IL-10-like inflammatory factors.[73] Foxp3 and RORγt are expressed by naive CD4$^+$T cells, and the cytokines of the microenvironment determine the direction of differentiation.[74] Studies have revealed that intestinal T cell homeostatic mechanisms are regulated by SCFAs, and SCFAs boost Treg formation and decrease Th17 production.[75] SCFAs increase Foxp3 activation by preventing histone deacetylase (HDAC). Foxp3 exon 2 regions directly interact with RORγt to prevent Th17 differentiation and promote Treg development. As a result, the amount of local IL-17 in the gut is significantly decreased, as is the intensity of intestinal inflammation.[76,77] A previous study has shown that intestinal SCFAs limit the pathogenicity of gut microbiota antigen-specific Th1 cells to preserve intestinal homeostasis and prevent the progression of colitis.[78]

A recent study has provided more evidence that SCFAs support intestinal immunoglobulin A (IgA) reaction.[79] According to Wu et al's study,[80] acetate increased intestinal IgA responses through the GPR43 receptor. Aldehyde dehydrogenase 1 family member A2 (Aldh1a2), which turns vitamin A into its metabolite retinoic acid, was expressed in DC due to acetate.[80] Additionally, blocking retinoic acid transmission prevented the induction of B cell IgA by acetate.[80] Butyrate, propionate, and acetate are crucial metabolites for preserving intestinal homeostasis.[81] Several studies have revealed that individuals with active IBD had lower fecal SCFA levels.[81] Significantly, not only do IBD patients have lower amounts of prominent SCFA-producing bacteria (such as _F. prausnitzii_ and _Roseburia intestinalis_) in their mucosal surfaces and feces, but their steady-state SCFA concentrations seem to be decreased as well compared to healthy individuals.[82,83]

SCFA topical treatment has been proven efficient in improving disease manifestations of UC patients.[84,85] Although butyrate was helpful for treating CD according to one uncontrolled pilot research,[86] no randomized controlled studies have been carried out. Additionally, most human studies have focused on the topical effects of butyrate, and limited data are presented here on how alterations in gut microbiota may be affected by the administration of SCFAs.[87] In this context, Lee et al[87] found that oral administration of butyrate or a combination of SCFAs affected T cell differentiation and gut microbial profiles but did not relieve dextran sodium sulfate (DSS)-induced colitis. To enhance the number of friendly and hostile gut microorganisms, SCFA administration boosted the expression of FOXP3$^+$Tregs and IL-17-producing T cells.

TABLE 1 Summary of clinical trials of microbiota-based therapies in inflammatory bowel disease (IBD)

Treatment	First author (publication year), country	Mechanism	Route	Descriptions
Butyrate	Di Sabatino[86] (2005), Italy	Butyrate inhibits NF-κB levels, which lowers the production of proinflammatory mediators generated by CD lamina propria mononuclear cells	Oral	Oral butyrate at a dose of 4 g/day for 8 weeks was beneficial in producing clinical recovery or disease remission and lowering ileocecal swelling in individuals with mildly to moderate active CD
Butyrate	Lührs[88] (2002), Germany	Butyrate-induced suppression of NF-κB stimulation in lamina propria macrophages in UC	Oral	A decline in NF-κB nuclear translocation in lamina propria macrophages is related to a noticeable improvement in clinical and histological markers in butyrate-treated UC patients. Because macrophage-derived cytokines primarily maintain the inflammatory process in UC, anti-inflammatory property of butyrate may be partly achieved by suppression of NF-κB recruitment in these macrophages
FMT	Rossen[180] (2015), Netherlands	Restore microbiota composition	Nasoduodenal tube	Fifty patients with mild to moderately active UC were allocated randomly to either one of the following two groups: those who received FMT with feces from healthy donors or those who received autologous fecal microbiota (control); each transplant was prescribed via nasoduodenal tube at the beginning of the study and 3 weeks later. UC patients who respond positively to FMT from a healthy donor have their aberrant microbiota restored to the healthy donor composition, whereas non-responders stay unchanged. No statistically significant difference in clinical and endoscopic remission was observed among UC patients who underwent FMT from healthy individuals and those who received their own fecal microbiota, which might be attributed to the small sample size. However, the microbiota of responders had distinct features from that of non-responders. This finding calls for additional research into the administration route, dosing, and matching of donors for selected patients. The reported changes in microbiota composition in responders could lead to data on choosing beneficial groups for donation rather than whole microbiome transplantation
FMT	Paramsothy[179] (2017), Australia	Increased microbial diversity	Enema	Intensive-dosing, multidonor FMT induces clinical remission and endoscopic improvement in active UC and is related to outcome-associated unique microbial alterations. As a result, FMT represents a viable new potential treatment for UC
FMT	Costello[255] (2019), Australia	Modifying colonic ecosystem	Enemas	In this trial of patients with mild to moderate UC, 1-week therapy with anaerobically prepared donor FMT contributed to a greater likelihood of remission at 8 weeks than autologous FMT
FMT	Moayyedi[178] (2015), Canada	Drive the immune response in UC	Enemas	FMT induces remission in a much higher proportion of patients with active UC than placebo, with no difference in adverse events. The fecal donor and the time of UC appear to affect patient outcomes
LBP	Seres Therapeutics[256] (2022), USA	Reduces gut inflammation	Oral	A multicenter, phase 2B, double-blind, randomized controlled, multi-dose trial was conducted to identify the effectiveness, safety, and microbiome modifications relating to the two recommended doses of SER-287 (Firmicutes spores) after pretreatment with vancomycin in adult patients aged 18–80 years with active mild-to-moderate UC
LBP	Janssen Research & Development, LLC[257] (2019), Belgium	Induction of Treg cell	Oral	The study's goal was to evaluate the safety profile of JNJ-72537634 to placebo in healthy volunteers following single and several daily doses

(Continues)

TABLE 1 (Continued)

Treatment	First author (publication year, country)	Mechanism	Route	Descriptions
LBP	4D Pharma plc[258] (2018), UK	Antagonizes NF-κB	Oral	This is single (Part A) and multiple dose (Part B) research. Ten eligible individuals were given a single dose of Thetanix or a placebo. A Safety Review Committee reviewed the safety data from these 10 participants up to Day 7 to evaluate its appropriateness to proceed to Part B, in which 10 participants took 15 doses of Thetanix or placebo twice daily for 7.5 days. In both trial stages, eight and two of the 10 individuals were given Thetanix or placebo at random. Each dose was made up of three capsules. Part B participants got the first and last doses in the clinic and took the remaining 13 doses at home. Subjects were required to answer health-related questionnaires at home and record their body temperature and when they consume the capsules in an electronic diary. Subjects who acquired a fever were subjected to further testing, such as blood cultures. Subjects gave fecal samples for microbiota and feces calprotectin analyses
Probiotic	San Giovanni Addolorata Hospital[259] (2021), Italy	NM	Oral	The purpose of this clinical study was to assess the efficacy and safety of LGG at two different doses for 1 month in UC patients with mild to moderate disease activity with oral mesalamin
Probiotic	VSL Pharmaceuticals[260] (2020), Italy	NM	Oral	The purpose of this phase IIa parallel-groups, randomized, double-blind, placebo-controlled trial was to assess the long-term effectiveness of two doses of VSL#3® supplemented with conventional therapy (5-ASA) in sustaining remission in an adult population of UC patients versus conventional treatment (5-ASA) plus placebo
Probiotic	Massachusetts General Hospital[261] (ongoing), USA	NM	Oral	A 12-week double-blind, randomized clinical trial of probiotic supplementation versus placebo was conducted to investigate the effect of a particular probiotic supplement on alterations in the gut microbiota, serum metabolomic profiling, and fatigue signs in individuals with quiescent IBD
Probiotic	Matsuoka[196] (2018), Japan	NM	Oral	For 48 weeks, 195 participants with quiescent UC were randomly assigned to receive one packet of B. breve strain Yakult fermented milk daily (B. breve strain Yakult 10 billion bacteria and L. acidophilus one billion bacteria) (n = 98) or matched placebo (n = 97). Compared to placebo, B. breve strain Yakult had no impact on time to relapse in UC patients
Probiotic	Palumbo[262] (2016), Italy	NM	Oral	Sixty patients with moderate-to-severe UC were assigned to receive mesalazine or mesalazine and a probiotic of L. salivarius, L. acidophilus and B. bifidus strain BGN4 for 2 years. The combination therapy showed a better improvement, even after two-year treatment, compared with mesalazine alone
Probiotic	Tamaki[263] (2016), Japan	NM	Oral	A randomized, double-blind, placebo-controlled study was carried out to assess the effectiveness of B. longum 536 (BB536) supplements in inducing remission in 56 Japanese patients with mild to moderately active UC. After 8 weeks, supplementation with BB536 was well tolerated and decreased UCDAI scores, EI, and Mayo subscores compared with controls.
Probiotic	Tursi[191] (2010), Italy	NM	Oral	VSL#3 supplements were safe and effective in reducing UCDAI scores in patients with relapsing mild-to-moderate UC using 5-ASA and/or immunosuppressants. Furthermore, after 8 weeks of treatment, VSL#3 improved rectal bleeding and appeared to re-induced remission in these patients; however, these variables did not achieve statistical significance.

TABLE 1 (Continued)

Treatment	First author (publication year), country	Route	Mechanism	Descriptions
Probiotic	Sood[193] (2009), India	Oral	NM	A multicenter, randomized, double-blind, randomized controlled trial of a high-potency probiotic, VSL#3, for the treatment of mild-to-moderately active UC was conducted. VSL#3 is both safe and effective in inducing clinical responses and remissions in these individuals.
Probiotic	Bourreille[264] (2013), France	Oral	S. boulardii is a probiotic yeast that has been found to improve the intestinal barrier and gastrointestinal immune system	S. boulardii might be utilized to cure CD patients. This randomized, placebo-controlled trial was conducted to assess the benefits of S. boulardii in CD patients who achieved remission while receiving steroid or aminosalicylate treatment. Although the probiotic yeast S. boulardii for 52 weeks is safe and well tolerated, it does not seem to benefit individuals with CD who are in remission following steroid or salicylate therapy
Probiotic	Bousvaros[265] (2005), USA	Oral	NM	This randomized, placebo-controlled trial on LGG was to evaluate whether adding LGG to routine treatment extended remission in children with CD. The findings of this study do not encourage LGG as an adjunctive treatment in stable individuals with CD who are already on maintenance medication. Further placebo-controlled study is needed to fully understand probiotic's possibilities in CD
Probiotic	Matthes[266] (2010), Germany	Enemas	Modulation of intestinal microflora	Clinical efficacy and dosage dependence of E. coli Nissle enemas for UC were studied. Compared to the intent-to-treat group, the effectiveness of rectal E. coli Nissle application was considered in the per-protocol population, indicating that E. coli Nissle is a well-tolerated therapy in moderate distal UC
Probiotic	Miele[267] (2009), Italy	Oral	NM	Twenty-nine patients with recently diagnosed UC was randomly assigned to receive either VSL#3 or placebo in addition to concurrent steroid initiation and mesalamine maintenance therapy, showing the effectiveness and safety of a highly concentrated blend of probiotic bacterial strains (VSL#3) in active UC and its role in remission maintenance
Probiotic	Rembacken[268] (1999), UK	Oral	NM	A recent study examined whether giving a nonpathogenic strain of E. coli (Nissle 1917) was as beneficial as mesalazine in suppressing UC relapse, showing that therapy with a nonpathogenic E. coli has the similar effect as mesalazine on sustaining UC remission. The positive effects of live E. coli may reveal information about the etiology of UC
Probiotic	Schultz[269] (2004), Germany	Oral	NM	Eleven individuals with moderate to active CD were included and randomly assigned to receive LGG (2×10^9 CFU/d) or a placebo for 6 months. The authors failed to establish an advantage of LGG in inducing or sustaining medically induced remission in CD.
Probiotic	Kruis[270] (1997), Germany	Oral	NM	A hundred and twenty participants with inactive UC were involved in a 12-week double-blind, double-dummy trial assessing the efficacy of mesalazine 500 mg t.d.s. to an oral formulation of live E. coli Nissle (Serotype 06: K5: H1) in avoiding disease recurrence. According to the findings of this early investigation, probiotic medication seems to give another alternative for UC maintenance treatment.

Abbreviations: 5-ASA, 5-aminosalicylic acid; B. Bifidus, Bifidobacterium Bifidus; B. breve, Bifidobacterium breve; CD, Crohn's disease; E. coli, Escherichia coli; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; L. acidophilus, Lactobacillus acidophilus; L. acidophilus, Lactobacillus acidophilus; L. rhamnosus, Lactobacillus rhamnosus; L. salivarius, Lactobacillus salivarius; LBP, live biotherapeutic product; LGG, L. rhamnosus GG; NF-κβ, nuclear factor kappa B; t.d.s, total dissolved solids; UC, ulcerative colitis; UCDAI, UC disease activity index.

SCFAs may serve as supplemental medication in the future treatment patients with active IBD and idiopathic colitis.[81] Both clinical and histological improvements have been shown in patients with active UC and diversion colitis after receiving enemas with butyrate or SCFA formulations.[88–90] Butyrate substances reduce nuclear translocation of nuclear factor kappa B (NF-κB) in lamina propria macrophages histologically in patients with UC, and cytokine production, and NF-κB activation in peripheral blood mononuclear cells (PBMCs) and lamina propria mononuclear cells from CD subjects.[88]

Only a small proportion of patients with UC had a therapeutic outcome after receiving SCFA enemas (40 mmol/L butyrate, 30 mmol/L propionate, and 100 mL of 80 mmol/L acetate twice a day for 6 weeks).[91] There is no correlation between the administration of butyrate enemas (60 mL of 100 mmol/L once daily for 20 days) and changes in daily symptomatology ratings, despite a slight influence on inflammatory markers, stool quality, frequency (Bristol stool scale) or oxidative stress, in UC subjects in clinical remission and is not associated with an improved prognosis.[92] In addition, patients with diversion colitis who were given SCFA enemas showed no signs of endoscopic or histological improvement.[93]

SCFA supplementation has inconsistent effects in mouse models of colonic inflammation. SCFA enemas, for instance, did not stop or lessen gastrointestinal injury in TNBS-induced rat colitis model.[94] While butyrate ameliorated colonic damage, and serum inflammatory mediators (IL-6, TNF-α, and IL-1) in mice with colitis induced by DSS,[95] although butyrate did not reverse or mitigate DSS-induced gastrointestinal injury in antibiotic-treated mice.[96] Moreover, in the TNBS-induced colitis murine model, butyrate became less efficient than live *F. prausnitzii* or its supernatant in an anti-inflammatory reaction. Despite this, both of them were able to increase IL-10 while simultaneously decreasing TNF-α and IL-12 levels.[44] Surprisingly, oral administration of SCFA-producing *Clostridium butyricum* derivative, commonly known as "supernatant", decreased colonic mucosal damage caused by DSS.[97] This discrepancy between butyrate and SCFAs may be species-specific or due to different colitis models (DSS vs TNBS), degree to which commensal bacteria are reduced, the amount of butyrate administration, or the administration route.

In CD-based simulations, adding butyrate-producing bacteria, particularly *Butyrococcus pullicaecorum*, increased epithelial barrier integrity.[98] In healthy subjects, the safety and tolerability of *B. pullicaecorum* were favorable.[98] However, the ability of butyrate to suppress gene expression in inflammatory processes was more vital in noninflamed controls, as evidenced by the cultivation of butyrate to inflamed biopsies from UC patients and noninflamed biopsies from controls.[99] Additionally, TNF-α has been reported to decrease responsiveness of intestinal epithelium to butyrate, which may compromise the potential usefulness of the drug in IBD patients with inflammation and instead recommend a preventive therapy to avoid disease flare-up.[100]

Jaworska et al[101] demonnstrated enhanced gut-to-blood penetration of SCFAs in both pediatric IBD patients and an animal model. These observations can pave the way to the development of a novel, noninvasive diagnostic instrument for conditions including IBD and necrotizing enterocolitis, which are characterized by intestinal barrier malfunction, as well as extraintestinal conditions characterized by impaired gut–blood barrier. The current approach to IBD diagnosis and follow-up comprises routine monitoring of intestinal inflammation based on clinical symptoms, laboratory indicators, and radiographic, endoscopic, and histological findings. As previously stated, anti-inflammatory actions need consistent synthesis and transport of SCFAs to the mucosa. As a result, the efficacy of SCFAs in restoring mucosal barrier equilibrium may be enhanced by increasing or restoring SCFA-producing bacteria using prebiotics or probiotics.

4.2 | UroA and IBD

UroA has attracted increasing attention as a potential treatment with anti-inflammatory and antioxidant properties.[102] Intestinal microbiota produces urolithins (organic polyphenolic compounds) from ellagic acid (EA) and ellagitannins (ETs).[103] EA is a type of ET that has been hydrolyzed and is high in pomegranate, berries, and nuts.[103] Humans cannot adequately ferment complex nutritious EAs and ETs, as digested by gut bacteria, resulted in a urolithin sequence.[104] Among all the urolithin species, UroA is the major metabolite in human.[105] In recent years, polyphenolic compounds have been found as potential anti-inflammatory nutritional components.[106,107] Many experiments have demonstrated that UroA has anti-inflammatory, antioxidant, estrogen regulator, antiproliferative, antibacterial, and neuroprotective properties.[103,108–112] Furthermore, therapeutic benefits of ET-rich dietary sources and medicinal plants have recently been reported in IBD.[113] Mechanism of UroA functioning is constantly changing and developing. As for anti-inflammatory characteristics, UroA is thought to function by inhibiting various signaling pathways, including phosphoinositide 3-kinase (PI3K)/Akt/NF-κB, nuclear factor erythroid 2-related factor 2 (Nrf2), and mitogen-activated protein kinase (MAPK)/NF-κB.[114]

Larrosa et al[115] evaluated the effectiveness of pomegranate extract (PE) and UroA in treating DSS-induced colitis, and found that PE and UroA decreased inflammatory indicators in the colonic mucosa including inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX2), prostaglandin E synthase, and prostaglandin E2, and altered the gut microbiota beneficially. Both PE and UroA upregulated the G1 to S cell cycle.[115] Several pathways, such as the inflammatory response, were shown to be downregulated in the UroA group. PE, but not UroA, was shown to lower oxidative stress in both plasma and colon mucosa. However, only UroA preserved its colonic architecture. During the course of inflammation, natural urolithin formation in PE-fed rats has been restricted. These data suggest that UroA, an anti-inflammatory molecule, is probably the most effective anti-inflammatory chemical available for healthy adults.

In contrast, nonmetabolized ellagitannin-related fraction may be responsible for the inflammatory response in the colon.[115] Zhang et al[116] investigated the effect of UroA on the involvement of immune cells in the colitis model, showing that UroA treatment for murine CD4$^+$T cells significantly reduced store operated calcium entry

(SOCE) in CD4$^+$T cells, which was followed by a significant decrease in the levels of Orai1 and stromal cell-interaction molecule (STIM) 1/2 transcripts and proteins. As previously reported, UroA treatment in a dose-dependent manner also increased the amount of microRNA (miR)-10a-5p in CD4$^+$T cells. Upregulation of miR-10a-5p in CD4$^+$T cells leads to significant reduction in STIM1/2 and Orai1 mRNA and protein levels, as well as SOCE. Additionally, UA inhibited the proliferation of CD4$^+$T cells. The effect of UroA and its powerful synthetic counterpart (UAS03) on intestinal barrier function was investigated in recent research by Singh et al.[15] The outcomes of this study show that UroA/UAS03 significantly improves the intestinal barrier function while also inhibits excessive inflammation in the gut. It has been demonstrated that the activation of aryl hydrocarbon receptor (AhR)-Nrf2-dependent pathways by UroA and UAS03 upregulates epithelial tight junction proteins.[15] In addition to anti-inflammation, therapy with these drugs has been shown in preclinical investigations to decrease the incidence of colitis by improving barrier dysfunction. In summary, these findings show that microbial metabolites have two-pronged therapeutic potential in the gastrointestinal tract, enhancing barrier function and reducing systemic and local inflammation to protect against colonic inflammation.

4.3 | BAs and IBD

BAs are the end products of cholesterol catabolism and play a role in the gastrointestinal absorption of nutrients and transportation of toxic metabolites, xenobiotics, and lipids via the biliary system.[117–119] In addition to regulating the enterohepatic circulation of these compounds, farnesoid X receptor (FXR) regulates their production as well.[120,121] The pathogenesis of BAs in chronic IBD remains unknown.[122] BA malabsorption (BAM) plays a crucial role in diarrhea, leading to secretion of water and electrolytes in the colon and induces propagated contractions.[122] IBD is primarily caused by inflammatory processes in the gut wall; however, abnormal BA metabolism and BA–FXR interplay play a role in the disease.[123]

Novel therapeutic approaches targeting BAs and their ligands or signaling have developed in recent years based on the pleiotropic function BAs serve in regulating gastrointestinal homeostasis and immunological responses.[124] It is possible to use pharmaceuticals that target BA transporters and ligands or indirectly change the signature of BA pool for a wide range of disorders. IBD is often accompanied by gut dysbiosis.[125] Compared to the general population, patients with UC have a sixfold increased risk of developing colorectal cancer (CRC).[126,127] Several studies have revealed that the administration of probiotics has the potential to improve mucosal barrier function and restore intestinal microbiota by altering the profile of the luminal BA pool.[128–130] According to animal studies, such treatment may also be used to effectively manage gastrointestinal disorders. For example, secondary BAs may be produced under the influence of *Lactobacillus johnsonii* La1 bile salt hydrolase (BSH) to prevent Giardia growth by poisoning the parasite.[131] Furthermore, 7α-dehydroxylating activity of *Clostridium scindens* established a BA signature that inhibits

Clostridium difficile infection.[132] Trials on drugs have focused on the specific BA receptors FXR and G protein-coupled BA receptor 1 (GPBAR1). PX-102, Ec001, LJN452, and GW4064 are some of the particular agonists that have been reported so far. EYP001 (PXL007), EDP-305, Px-102/104, TERN-101 (LY2562175), tropifexor (LJN452), MET409, cilofexor (GS-9674 or Px-201) (LMB763), WAY-450, AGN-242266 (AKN-083), OCA, and nidufexor are some of the documented FXR agonists that have under clinical trials. When GW4064, the first synthetic FXR ligand, was identified as a molecule in 2000, it was found to have a significant effect on abnormal bacterial growth in the small intestine and decreased intestinal permeability and inflammatory processes in mice.[133,134] Despite being widely utilized in research for many years because of its affinity for FXR, GW4064 was not developed into a medication due to its poor pharmacokinetics and limited plasma bioavailability.[135] For the treatment of primary biliary sclerosis (PBC) and nonalcoholic steatohepatitis (NASH), LJN452, also known as tropifexor, has advanced as a novel safe medication candidate that might activate FXR with beneficial features.[136,137]

BAs act as signaling molecules via GPCRs and activate nuclear receptors.[138] Triggering of these receptors modulates the expression of genes involved in several pathways, such as inflammation, BA balance, and lipid metabolism.[140] Immunomodulatory effects of BAs have been well studied in recent years. Innate immune cells and gut epithelial cells are shown to be immunoregulated by BAs via the activation of nuclear receptors pregnane X receptor (PXR), FXR, and vitamin D receptor (VDR).[138]

Nuclear transcription factor FXR (NR1H4) and the seven-transmembrane GPCR, GPBAR-1 (also known as TGR5), are the most-studied receptors.[139] TGR5-related BA receptor pathway might be vital in the regulation of epithelial barrier function.[139] TGR5 activation improves barrier function and prevents against bile leakage.[139] TGR5 only expresses in *Lgr5*-positive intestinal stem cells (ISCs) and its activation supports the reconstitution of *Lgr5$^+$* ISC required for epithelial healing in DSS-induced colitis in mice.[140] The BA receptor TGR5 is involved in the onset, progression and resolution of intestinal inflammation. BAs improve inflammation by stimulating TGR5 and nuclear receptors.[141] TGR5 is related to the induction and mitigation of inflammatory reaction. Bile reflux into the pancreatic duct is associated with acute pancreatitis, and TGR5 has been identified as a modulator of BA-induced pancreatitis.[142] TGR5 is expressed at the apical pole of acinar cells, and a retrograde ductal infusion of taurolithocholic acid-3-sulfate (TLCS) into the pancreatic duct caused pancreatitis in wild-type mice but not *Tgr5$^{-/-}$* animals.[142] BAs did not affect pathological calcium transients, intracellular activation of zymogens, or TLCS-induced cell injury.[142] A study has suggested that TGR5 has an immunosuppressive and anti-inflammatory activity.[143] Monocytes express TGR5 in peripheral circulation, differentiated macrophages, and dendritic cells, and TGR5 stimulation reduces the production of macrophage cytokine.[144,145] TGR5 increases intestinal macrophages in CD patients, and its activation suppresses TNF-α production.[144,145] *TGR5* gene, located on chromosome 2q35, is close to a genetic variant linked to primary sclerosing cholangitis (PSC), which is a chronic inflammatory disorder of the bile duct.[146] Further research is needed

to establish the role of TGR5 in inflammatory disorders of the gastrointestinal tract. TGR5, on the other hand, suppresses NF-κB-mediated inflammatory signaling, and *Tgr5*$^{-/-}$ animals present with increased lipopolysaccharide (LPS)-induced hepatitis, showing the relevance of this anti-inflammatory mechanism.[147,148] Specific FXR, PXR, or VDR agonists diminish the inflammatory reaction in experimental models of intestinal inflammation, but animals deficient for one of these receptors are susceptible to intestinal inflammation.[138] Moreover, FXR and PXR in mice impaired epithelial permeability, leading to colitis or ileitis.[149,150] As a result, changes in nuclear receptor signaling may have a considerable impact on intestinal inflammation.

Several experiments on therapeutics that target the BA–gut microbiota axis have been conducted based on the alterations and impacts of gut microbiota and BAs in IBD. Wang et al[151] revealed that a hydrolyzed protein diet helped alleviate chronic inflammation in a canine model, which was associated with increasing concentrations of lithocholic acid and deoxycholic acid and recovered gut microbiota, as evidenced by decreased infections and greater BA-producing *Clostridium hiranonis*. Fucose and the total alkaloids in *Sophora alopecuroides* L., two other food ingredients, also have some therapeutic benefits on mouse colitis.[151–153] They may improve gastrointestinal dysbiosis and enhance the Firmicutes/Bacteroidetes composition. Furthermore, the concentrations of primary and conjugated BAs decrease following therapy and are comparable to those of the control group.

Moreover, in cases with CD, exclusive enteral nutrition (EEN) might partially normalize the aberrant structure of BAs, resulting in higher lithocholic acid with decreased primary and conjugated BAs.[154] Remarkably, subjects with various BA profiles and microbial ecosystems respond differently to EEN. Subjects with primary BA as the dominant BA have either non-sustained remission or recurrence following EEN treatment. Gut microbial diversity is lowered, with decreased abundances of Ruminococcaceae and Lachnospiraceae and higher abundances of the phylum Proteobacteria. Trials on adults, on the other hand, have yielded varying findings, probably due to poor adherence to therapy.[155] Generally, nutritional treatment appears to be a pretty safe method.

Several investigations have connected BA dysmetabolism to gastrointestinal dysbiosis in IBD patients.[156,157] According to Devkota et al's study,[158] high-saturated-fat diet causes the growth of the pathobiont that produces hydrogen sulfide (H$_2$S), *Bilophila wadsworthia*, which in turn induces colitis in *Il10*$^{-/-}$ mice. Taurocholic acid is responsible for the proinflammatory impact of a high-saturated-fat diet.[158] It is well recognized that the sulfonic acid moiety in taurine, the conjugate in taurocholic acid, might be dissimilated by gastrointestinal microbiota-producing H$_2$S as a byproduct.[159] Diet rich in fat or meat causes additional taurine conjugation to BAs, resulting in more significant H$_2$S production, which is thought to be a risk factor for IBD.[158,160] Alternatively, IBD-related microbial dysbiosis might cause BA dysmetabolism, which might change how BAs operate as an anti-inflammatory agent.[156] Duboc et al[156] revealed that bacterial metabolism of BAs is defective owing to microbial dysbiosis. Furthermore, they demonstrated that this gastrointestinal dysmetabolism disrupted the intestinal BA pool, which influenced the anti-inflammatory

properties of BAs.[156] In fact, BAs are recognized as anti-inflammatory mediators that prevent NF-κB activation and, as a result, minimize macrophage cytokine secretion.[148] The relevance of deconjugation by gut microbiota is shown by the anti-inflammatory activity being specific to secondary BAs but not the conjugated ones.[156] Activation of BA receptors prevents against experimental colitis, and may also have an anti-inflammatory impact.[161] Mice lacking FXRs have reduced intestinal barrier and decreased antimicrobial protection in the small intestine.[133] Following the discovery of an association between IBD and *NR1H4* gene mutation, which codes for the FXR, the function of BAs in protecting against inflammatory response has recently been established.[162] A pilot study on fecal BA and microbiota profiles in IBD revealed that overall individuals with IBD and healthy controls had similar BA profiles.[163] SBAs have been demonstrated to improve phylum-level fecal dysbiosis associated with colitis and lessen its severity.[163] According to the most recent study, gut dysbiosis was found to cause a lack of SBAs in UC patients who are prone to inflammation. This results in a proinflammatory condition in the intestine, which may be addressed by restoring SBAs.[16] Similar to BA dysmetabolism, BA malabsorption is a prevalent cause of diarrhea in CD and colitis cases.[164,165]

It has been shown that probiotics (*Lactobacillus plantarum* CCFM8661, *Lactobacillus reuteri* NCIMB 30242, and VSL#3) affect BA metabolism in mice and human beings via FGF19/FGF15 by enhancing the production and excretion of BAs.[166–168] With higher bile salt hydrolase function, VSL#3 induced expansion of Bifidobacteriaceae and Lactobacillaceae, which reduced conjugated/deconjugated BAs.[168] To cooperatively repair the microbial composition and activity in IBD cases, bacterial consortia were developed. Main therapeutic activities, such as converting SBAs, particularly deoxycholic acid and lithocholic acid, were intended to be provided and replenished. Synbiotics—prebiotics combined with probiotics—are often used. Prebiotics may influence the formation of the microbial metabolites SCFAs and BAs in addition to promoting the development of probiotics, including Ruminococcaceae, Lachnospiraceae, and *Bifidobacterium*.[169–172] For instance, inulin raised deoxycholic acid and lithocholic acid levels in dog feces.[172] Overall, probiotics and prebiotics may regulate gut homeostasis by changing the bacterial and BA compositions and may contribute to the cessation of intestinal inflammation.

It has been recognized that the SBA ursodeoxycholic acid (UDCA) possesses therapeutic effects.[173] In 1997, Kullmann et al[174,175] demonstrated for the first time that UDCA had anti-inflammatory properties that protect against intestinal inflammation. In both the TNBS-induced colitis and indomethacin-induced ileitis models, oral treatment with UDCA lowered macroscopic and microscopic damage scores and reduced weight loss in rats.[174,175] The protective effects of UDCA and its taurine conjugate have been confirmed in numerous preclinical studies using a variety of chemically induced intestinal inflammation models, such as the colitis model induced by TNBS or DSS, enteritis model induced by indomethacin, and the chemotherapy-related mucositis model.[173] UCDA also protects against minor intestine inflammation in the mouse model of

nonalcoholic fatty liver disease (NAFLD), wherein mucosal inflammation is associated with a high-fat diet.[176] Another study on genetically engineered TNFARE (TNF$^{\Delta ARE}$ mice carry a genetic deletion in the AU-rich elements [ARE]) mice, a recognized model of CD caused by excessive TNF production, also reported an anti-inflammatory effects of UDCA and its conjugates.[138] Therefore, preclinical investigations in various disease models significantly support the notion that UDCA may effectively prevent or alleviate chronic intestinal inflammation in complement to its hepatoprotective properties.

4.4 | FMT in IBD

FMT has been reported to induce clinical remission in 33% of the 307 elderly subjects included in a meta-analysis of 24 UC cohort surveys. While the remission rate was decreased to 23% in six pediatric cohort studies involving 34 UC participants.[177] Randomized controlled studies have also shown favorable outcomes when using FMT to treat UC. A study included 70 individuals with UC, all of whom presented with active disease but no infectious diarrhea; after a maximum of 6 weeks, 24% of individuals who received FMT achieved remission compared to 5% of those who received a placebo. Both groups were taking anti-inflammatory/immunosuppressive medication (such as mesalamine, anti-TNF agents, and corticosteroids).[178] Similar findings were shown when employing enemas 5 days per week for 8 weeks in Australians, which found a remission rate of 27% in UC cases with active UC administered with FMT compared to 8% in those managed with placebo.[179] Subjects were given immunosuppressive medicines, including thiopurines, methotrexate, 5-aminosalicylates, and oral prednisone in a consistent dosage regardless of whether or not they had undergone FMT.[179] On the other hand, remission rate in UC cases treated using FMT from healthy individuals were comparable to that in those who received autologous fecal microbiota.[180]

On the other hand, therapeutic benefits of FMT in CD come from limited, uncontrolled research. Of patients whose symptoms were alleviated after receiving a single colonoscopic FMT treatment, 58% reported clinical response.[181] This was supported by increasing levels of Tregs in the lamina propria of the recipients, which was proceeded by high microbial diversity, indicating a reconstruction of microbial homeostasis and less evident inflammation.[181] Additionally, a single FMT resulted in clinical response and remission in CD patients, accompanied by an increased body weight of the patients.[182] A 12-week washout time was necessary for all CD patients who were subjected to immunosuppressive medications, including tacrolimus, infliximab, or cyclosporine. Traditionally, antibiotics and probiotics were discontinued 60 and 30 days before FMT.[181] The potential benefits of FMT in adolescent CD patients were also examined. Nine people aged 12–19 years with mild-to-moderate CD were given FMT using a nasogastric tube once and then observed for 12 weeks.[183] Regarding the clinical scoring, seven of the nine cases were in remission 2 weeks following FMT; while at 6 and 12 weeks following FMT, five were in remission. During the FMT or placebo therapy, all subjects included in the research were authorized to undergo immunomodulators.[183]

In a systematic review and meta-analysis by Colman and Rubin, a comprehensive evaluation of 18 trials that employed FMT as the primary treatment in 122 IBD patients was performed, showing an average remission rate of 45%.[184] A subgroup analysis revealed that CD cases were much more likely than UC cases to respond to FMT (60.5% vs 22%). This shows that recognizing and transferring particular bacterial communities to reestablish gut balance may significantly restore intestinal health.[178] Vomiting, postduodenal infusions and mild fever have been reported as side effects of FMT.[184] Serious adverse events are uncommon; however, flare-ups of IBD and infection have been documented.[185,186] Although all successfully conducted studies engaged one FMT protocol, it is essential to remember that this results in an extra burden on both the patient who require additional endoscopic examination and the health professional who imposes additional costs.

4.5 | Probiotics and IBD

Probiotics are defined as "living micro-organisms that, when consumed in a particular amount, provide health advantages in addition to natural basic nutrients".[187] According to the increasing evidence, probiotics appear to modify disease presentation in both animal models of and patients with IBD.[188] The results are likely to be minor at best, which may be due to the probiotic microorganism chosen, the diversity in organism doses delivered, and the heterogeneity of the conditions being addressed. Probiotics have been employed successfully in treating IBD to reduce dysbiosis in cases receiving long-term antibiotic or immunosuppressive therapy.[189] Furthermore, these bacteria have been exploited as an adjuvant treatment to reverse the dysbiotic milieu linked to the formation and progression of IBD.[189] Despite many experiments and clinical studies using probiotics for the treatment of IBD, lack of standard procedures during therapeutic protocols, limited sample sizes, and inadequate illness identification have restricted the valuable findings of probiotic in this situation.

Probiotics have been identified as an option for inducing and maintaining remission in UC, while those in CD show little or no benefit.[190] Adjuvant administration of multispecies probiotic VSL#3 comprises four strains of *Lactobacillus casei*, *L. plantarum*, *Lactobacillus acidophilus*, and *Lactobacillus delbrueckii* spp. *Bulgaricus*, three of *Bifidobacterium longum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, and one of *Streptococcus salivarius* spp. *thermophilus*, upon consuming a daily dosage of 3.6×10^{12} colony-forming units (CFUs), participants with mild to moderately active UC achieved clinical remission.[191,192] Corroborating findings were obtained following managing mild to moderately active UC patients with VSL#3 alone twice a day at the exact dosage as previously stated.[193] The rate of remission maintenance in UC patients treated with either nonpathogenic *Escherichia coli* Nissle 1917 (EcN) or mesalazine were likewise comparable.[194]

Adjuvant treatment with *Bifidobacterium*-fermented milk (including *L. acidophilus*, *B. breve*, and *B. bifidum*) for 12 weeks (10 billion bacteria/d) improved clinical and endoscopic activity index in 20 patients who had mild to moderately active UC compared to placebo.[195]

Notably, the levels of SCFAs in stool were increased in the probiotic-treated group than in the placebo group. Nevertheless, a current experiment utilizing a similar therapeutic regime (fermented milk including *B. breve* and *L. acidophilus*) found no effect in treating or maintaining UC remission in 195 participants.[196] In fact, using *B. bifidum* (as a single strain-containing probiotic) might enhance fecal SCFA concentrations in healthy individuals; nevertheless, the preventive effect in UC or CD remained unclear.[197] The first study was the only one to confirm the extraordinary development of *Bifidobacteria* in the feces of probiotics-treated patients and to undergo endoscopic inspection, despite the fact that other studies included significantly fewer participants. Therapy with *Lactobacillus* GG alone or combined with mesalazine prolonged the relapse-free period in UC patients in a treatment regimen that lasted 12 months. This was in comparison to the group that was treated with immunosuppressants alone.[198]

In vivo rodent colitis models enable researchers to investigate the influence of microbiota, mainly probiotics, on inflammatory response in colon and serve as a model to investigate their potential health-promoting impacts in IBD or other illnesses linked to intestinal mucosa swelling.[199] To find in vitro signs that may predict advantages, several researchers have attempted to correlate these in vitro and in vivo preclinical outcomes. For example, in an experimental murine colitis model, Foligne et al[200] suggested that the ratio of anti-inflammatory and proinflammatory mediators (IL-10 and IL-12) generated by PBMCs following their in vitro stimulation by probiotic strains might anticipate their beneficial influence in vivo. The ratio of IL-1β proteins and the IL-1β receptor antagonist in specimens from IBD patients were shown to be different from those in tissues of healthy control animals.[201] Although there was no absolute change in IL-1 mRNA or protein, there may have been a rise in inflammatory signals fueled via IL-1β in animal IBD.[201] Nishitani et al[202] used a mouse model of DSS-induced colitis to assess the in vivo anti-inflammatory effects of *Lactococcus lactis* subsp. *cremoris* FC. No discernible variations in weight loss between *L. lactis* subsp. *cremoris* FC-treated and -untreated mice were seen throughout the DSS modeling, which was combined with oral administration at a concentration of 3% and given ad libitum for 5 days. However, mice given *L. lactis* subsp. *cremoris* FC showed considerable improvement in shortening of colon length. Additionally, as contrasted with mice that were not treated, *L. lactis* subsp. *cremoris* FC-treated mice had substantially reduced histological scores for the intensity of inflammation, thickness of inflammatory cell infiltration, and extent of lesions.[202] Taken together, probiotics appear to be ineffective in CD in terms of inducing and maintaining remission in mild to moderately active UC. There is insufficient information to draw definitive conclusions from the study results. More randomized, double-blind, placebo-controlled, multicenter investigations are needed.

4.6 | LBPs and IBD

Considering the length of remission in certain disorders, the benefits of FMT go beyond the transitory transplanting of pharmacological effector molecules from donor to recipient in the FMT mixture.[203]

Certain donor strains might help reduce disease severity in FMT.[179] Host–microbe interactions throughout the gastrointestinal tract that have immunomodulatory impacts on human health have attracted much attention.[204-206] The colonization of wild-type microbiota species or modified bacterial strains in a gnotobiotic mouse model is widely used.[207] Polysaccharide A (PSA), as generated by the symbiont *Bacteroides fragilis*, defends against *H. hepaticus*-induced colitis.[208] *H. hepaticus* causes colitis and proinflammatory cytokine secretion in animals carrying *B. fragilis* that do not produce PSA.[208] In parallel to *B. fragilis*, other gut-resident bacteria such as Clostridiales have been shown to activate Treg cells or signal transduction pathways, including AIEC, segmented filamentous bacteria, and *Citrobacter rodentium* modulation of the colitogenic Th1 and Th17 reactions.[209-211] As a result, using LBPs that either enhance anti-inflammatory processes or block proinflammatory processes could be an approach for restoring equilibrium and immunological tolerance in the gut.

LBP refers to living organisms engineered and produced to cure, alleviate, or prevent illness in individuals.[212] The primary distinction between probiotics and LBPs is their labeling in terms of regulatory claims; nevertheless, certain probiotics may be categorized as LBPs following root canal treatment and fulfillment of certain requirements.[213] As a treatment, LBPs could be supplied as latent spores, microencapsulations, or entire freeze-dried bacteria, and they are designed to live in the gut indefinitely.[212] The capacity of LBPs to constantly release effector molecules on site in particular niches in the gut where they persist, preventing injection of vast dosages of bioactive components is one of its benefits over purified molecules.[214] Furthermore, issues remain over competitive efficiency with the endogenous microbiota, and the toxicity of injecting living microbes persists. There are currently no licensed LBPs for use in the treatment of IBD, though clinical trials are under way. EcN was not initially categorized as a LBP, which is one of the first live probiotic strain used to manage IBD.[203] This nonpathogenic Gram-negative strain is a well-studied probiotic that produces components, including microcins, adhesins, and proteases, probably aid in its longevity and the colonization in the human digestive system, which generally requires several days.[215] Now, lyophilized EcN is introduced to the market under the brand name Mutaflor® and is the only probiotic recommended by the Second European Consensus an efficient alternative to mesalazine in the maintenance of disease remission in UC.[216] According to a meta-analysis in 2015 that included six studies, EcN induced remission in 61.6% of patients with UC, which was similar when compared to mesalazine (69.5%).[217] Germany, Canada, Singapore, Australia, and New Zealand are among the nations where EcN is authorized and available as a probiotic. Its possibility as a LBP for extended IBD therapy are being investigated in greater depth, and preclinical genetically engineered experiments on EcN are being conducted.[216-218] Two double-blind randomized controlled trials investigated the role of LBPs in IBD.[203] Both single-strain treatment like *Lactobacillus* GG and multistrain cocktails, including *Bifidobacteria*, have inconclusive outcomes.[219-221] A meta-analysis indicated that probiotics were more beneficial than placebo in sustaining remission in UC; nonetheless, the findings were no better than those obtained

under traditional therapies like 5-ASA or mesalazine.[222] Therefore, these older-style probiotics do not demonstrate promising outcomes in treating or maintaining remission in IBD, so research into LBPs, particularly anaerobic strains, has been conducted.

A combination of 17 Clostridia strains is now under phase 2 studies to manage UC and CD. The strains promote Treg cell accumulation in the gut mucosa.[45,46] This consortium combination was revealed using a top-down gnotobiotic method, which involved transferring human-derived fecal microbiota into germ-free mice after chloroform therapies (which eliminates all but spores), followed by subsequent mouse-to-mouse transfers while choosing for the particular anti-inflammatory Treg development.[45] In conjunction with Vedanta, Seres Therapeutics promotes the development of SER-287, a consortium of several *Firmicutes* spores which has been evaluated in a phase 2 study.[223] SER-301, a more contemporary LBP that has reached phase 1 trials, consists of a collection of 18 live human commensal bacterial strains isolated and grown from the feces of healthy volunteers. In complement to these consortium strain mixes, single-strain LBP *Bacteroides thetaiotaomicron* (Thetanix) has shown improved mucus formation in the colon of gnotobiotic animal models and is being promoted for the management of IBD by 4D Pharma.[224] When it comes to clinical investigations and regulatory licensing of LBPs, the provenance of the strains utilized in these "living medicines" is considered critical. The regulation considerations on this subject have changed recently and are an ongoing process.[225] Authorities are likely to evaluate strains separated from feces differently than genetically altered ones, and the Food and Drug Administration (FDA) now needs further checks to confirm the stability of their genetic alterations.[226] Genetically modified strains are anticipated to face considerable regulatory challenges in Europe and other countries where current restrictions on the use of genetically modified organisms (GMOs) would be a significant barrier. Since many attempts have been made to improve the understanding of the complexities of strain engraftment, a limited ability to forecast bacterial engraftment in distinct individuals with diverse microbiomes constitutes one of the leading obstacles in the progression of LBPs into the phase 2/3 clinical trials.[227]

4.7 | Phages therapy for IBD

Phage therapy refers to manipulating a person's phageome and, as a result, bacteriome when such individual suffers from a condition that is assumed to have a bacterial cause.[228] Typically, it entails multiple stages, including alteration of the genetic material of an existing phage in a manner that provides effective adhesion to the preferred strain of bacteria, generation of one or more phage strains depending on the situation, and use of a dosage regimen for the patient, as well as administering the phage preparation to the patient.[228]

Since phage treatment seems to be a relatively novel concept, mainly due to the rise in antibiotic resistance, it was first introduced in the 1920s by Félix d'Hérelle who successfully treated patients suffering from illnesses such as dysentery and cholera.[229] On the other hand, a broad use of antibiotics overwhelmed phage treatment decades later. Even now, resistance to antibiotics is the primary reason why phage

therapy is considered a viable alternative treatment option.[230,231] Utility of phage treatment in IBD and the pivotal role played by intestinal microbiota in the development of the disease are being studied as microbiome change by the targeted bacterial species.[228] Additionally, there are two potential mechanisms by which phages might influence the reaction of the host to their presence and vice versa. Immune reaction to the contents of the phage particles reflects direct action on the part of the host.[228] Indirect action is shown by horizontal genes delivered from phages to bacteria.[228]

A vital concern of potential phage treatment for IBD that must be addressed is whether phages stimulate the immune system of the host in a manner that causes aberrant immune function.[231] Any phage designed for phage treatment must be immune system–insensitive. Numerous investigations have shown that phages may increase antibody production.[232] Phage treatment may still have a potential effect notwithstanding antibodies and a higher incidence of phage inactivation.[233] An experiment on GF mice found that phage therapy led to an increased number of immune cells in the gut. Pattern recognition receptors, which mediate the innate immune response, were shown to induce interferon (IFN)-γ in response to *Lactobacillus, Escherichia*, and *Bacteroides* phages through Toll-like receptor (TLR)-9.[228] Furthermore, UC subjects who responded to FMT had quite a lower amount of phages than non-responders, and mucosal IFN-γ levels were shown to be directly associated with the number of phages in the mucosa.[228] In addition, researchers have revealed that phages from patients with aggressive UC elicited a more robust IFN-γ expression than those from healthy controls.[234]

Based on these observations, it is possible to conclude that phages negatively impact the gut environment.[228] Additionally, they may also have anti-inflammatory properties. The T4 phage was shown in one study to have immunomodulatory properties, as measured by its ability to reduce the formation of reactive oxygen species (ROS).[228] ROS production in stimulated peripheral blood polymorphonuclear leukocytes by LPS or strains of *E. coli* was decreased by this phage.[235] Using mouse models, researchers have demonstrated that the T4 phage attenuated the migration of immune cells into an allogeneic skin graft, T cell development, and NF-κB activation.[236] *Staphylococcus aureus* phage has recently been shown to influence NF-κB activity.[237] The ubiquitous existence of phages in human may significantly suppress immune function and establish inflammatory or autoinflammatory conditions, including IBD.[238] Even in healthy individuals, according to Górski et al's findings,[236] phage can cross the mucosa and enter the systemic circulation. This shift might have immunomodulatory properties.

Interestingly, the amount of viral particles in the blood rises when mucosal membrane is impaired throughout the inflammatory response, and intestinal vulnerability increases. Nevertheless, the mechanisms of phage immunity regulation remain unknown.[239] Furthermore, accelerated destruction of bacterial cells by lytic phages may result in an overabundance of proteins, LPS, and nucleic acids, possibly promoting inflammation significantly.[240]

Though not categorized as LBPs, bacteriophages targeting specific kinds of bacteria have now been investigated as a therapy to modify

microorganisms associated with IBD.[203] AIECs, which are extremely common in ileal CD (ICD), have been found to be significantly reduced by bacteriophage treatment in preclinical studies.[241,242] Intralytic EcoActive bacteriophage targets AIECs and is now at the stage of patient recruitment of phase 1/2a study to investigate its safety and effectiveness for CD patients. BiomX has created another bacteriophage cocktail for the management of IBD. Candidate of _Klebsiella pneumoniae_, a Gram-negative opportunist bacterium linked to initiating and worsening primary sclerosing cholangitis and IBD, BX003 is also under investigation.[243] Bacteriophages are self-replicating viruses that are assumed to be inert to mammalian cells. They are frequently considered potent antibacterial compounds for IBD treatments; nonetheless, these medicines' "live therapy" character poses a significant regulatory obstacle to overcome. Bacteriophage-based treatments may have more focused effects than antibiotics, which are still applied in medical setting to treat IBD in a somewhat non-specific manner, and they may alleviate some of the possible engraftment concerns related to LBPs.

5 | MICROBIOME-BASED COMBINED TREATMENT

Experiences gained from the treatment for cancer have demonstrated that medication interactions or patient variation can account for the effectiveness of combination therapy (ie, drug independence). An increase in potential effectiveness of medication may be attributed to a synergistic or additive impact, and the combination only increases patient's probability of responding to a single medicine.[244] It has been proven that combining anti-TNF agents with immunosuppressants (thiopurines or methotrexate) can enhance anti-TNF pharmacokinetics in IBD.[245] Additionally, probiotics may be effective for the prevention of postoperative CD recurrence when used in conjunction with antibiotics.[246] Probiotics given along with iron supplements may protect against DSS-induced colitis; remarkably, EcN outperformed pathogenic bacteria.[247] Combining probiotics with iron supplements help improve iron absorption. A preliminary study showed that consuming freeze-dried _L. plantarum_ 299v with a meal prepared to maximize iron bioavailability improved iron absorption.[248] In this situation, clinicians may recommend probiotics along with iron supplements.

A randomized experiment was conducted by Campieri et al[246] to determine the effectiveness of rifaximin combined with the probiotic product VSL#3 in preventing postoperative relapse of CD. In 40 patients who had had curative resection for CD, rifaximin (1.8 g/d) for 3 months was matched with mesalazine (4 g/d) for 12 months. The rate of severe endoscopic relapse had been considerably decreased with the antibiotic–probiotic combination compared with mesalazine alone (2/20 [10%] vs 8/20 [40%]). This difference persisted throughout the trial (4/20 [20%] vs 8/20 [40%]).[246]

Furthermore, a probiotic and prebiotic combination therapy using _psyllium_ (_Plantago ovata_), _B. longum_, _L. casei_, and _Bifidobacterium breve_ significantly decreased a daily occurrence of diarrhea and the stomach pain index.[249] Traditional Chinese medicine (TCM) and probiotics work

better together to reduce IL-8 expression and prevent neutrophil recruitment, although they may not substantially affect the IL-6-macrophage-TNF-α pathway.[250] C-reactive protein (CRP) is considerably lowered following probiotics and TCM therapy. In contrast, IL-10 functions in UC as an anti-inflammatory cytokine. The incidence of spontaneous colitis was related to IL-10 as well as IL-10R deficiency.[251] Probiotics' ability to reverse the effects of TCM and IL-10 shows that they have an anti-inflammatory impact on the gut.[250] Probiotics used in conjunction with other medications can increase clinical effectiveness for treating IBD, lower the risk of recurrence and side effects, indicating that the combination therapy may confer a significant therapeutic benefit. The therapeutic benefits of probiotics and anti-IBD agents are enhanced by their combination. For the management of severe CD of the ileum and proximal colon, Steinhart et al[252] evaluated the use of budesonide, a glucocorticosteroid that is approximately as efficacious as prednisolone but without steroid-associated side effects, and found that adding ciprofloxacin and metronidazole to budesonide was an inefficient strategy in individuals with active CD of the ileum, but might enhance outcomes when the colon was involved.

Additionally, VSL#3 with Lactobacillus significantly improved clinical outcomes in children with IBD.[253] Also, Lactobacillus probiotics with prebiotics are significantly effective for UC.[253] Novel therapeutic approaches may reverse changes in SCFA levels related to dysbiosis and loss of microbial diversity in IBD, particularly noticeably in CD patients.[254] Although the effectiveness of fecal microbiota obtained from healthy donors in UC have been reported,[177] it is still necessary to verify the stability and safety of such treatment over the long term. Prebiotics and fiber-rich meals with probiotics are two more strategies for microbiome restoration. SCFA-producing single microorganisms or combinations may reduce symptoms by raising butyrate levels. Combining various microbiome-based treatments with other non-microbiome-based treatments while being guided by syndrome distinction is a useful method to boost clinical effectiveness. However, further studies are still required to assess the long-term efficacy and safety of microbiome-based treatments like probiotics combined with anti-IBD medications to treat IBD.

6 | CONCLUSIONS

Growing evidence implies that the causality of IBD is complicated and multifactorial, including genetic background, environmental factors, alteration in the gut microbiota, immune dysregulation, and their interactions. In addition, several studies have demonstrated the critical role of gut microbiota and their metabolites in host physiological systems, such as immunological, metabolic, neurological, and nutritional homeostasis. Modifications in the gut microbiota composition and abundance have long been linked to chronic inflammatory responses; however, a particular cause-and-effect link between gut dysbiosis and IBD has proven to be challenging to establish, particularly in humans. Animal studies have clarified critical immunological mechanisms in the pathophysiology of IBD, verified the proinflammatory and anti-inflammatory activities of gut microbiota, and

demonstrated that gut microbiota is essential for the establishment across most colitis models. Many efforts are being made to treat IBD using microbiome-based therapies, such as probiotics, prebiotics, FMT, LBPs, microbial metabolites (SCFAs, UroA, and BAs), and phage therapy. For instance, in several clinical trials, FMT achieved significant remission in patients with IBD; nevertheless, it should be highlighted that it is related to the risk of transferring additional infectious pathogens from donor to recipient. With regard to IBD, a majority of studies to date have focused on the influence of butyrate, hinting at a prebiotic or probiotic therapy. Although acetate may be a more effective target, reestablishing dysbiosis in CD and UC by increasing the colonization of butyrate-producing microbes is encouraging. Another exciting finding for treating IBD is a microbial metabolite called UroA. Animal study showed that this metabolite might alleviate IBD by enhancing tight junction proteins and decreasing gut inflammation; however, clinical trials are warranted to determine metabolite behavior in human.

In conclusion, microbe-based therapeutics will certainly play a part in the future treatment of IBD; nevertheless, numerous issues remain regarding bacterial diversity, timing of treatment, and patient selection for such therapies. Ultimately, further research is urgently needed to characterize host–microbe interactions in the disease and patient's response to treatment modalities.

CONFLICTS OF INTEREST

The authors had no conflicts of interest to declare.

ORCID

Rasoul Mirzaei https://orcid.org/0000-0002-4148-6495

REFERENCES

1. Kudelka MR, Stowell SR, Cummings RD, Neish AS. Intestinal epithelial glycosylation in homeostasis and gut microbiota interactions in IBD. *Nat Rev Gastroenterol Hepatol.* 2020;17(10):597-617.
2. de Souza HSP, Fiocchi C. Immunopathogenesis of IBD: current state of the art. *Nat Rev Gastroenterol Hepatol.* 2016;13(1):13-27.
3. Salas A, Hernandez-Rocha C, Duijvestein M, et al. JAK–STAT pathway targeting for the treatment of inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol.* 2020;17(6):323-337.
4. Lefevre PLC, Vande Casteele N. Clinical pharmacology of Janus kinase inhibitors in inflammatory bowel disease. *J Crohns Colitis.* 2020;14(Suppl):S725-S736.
5. Monteleone G, Fina D, Caruso R, Pallone F. New mediators of immunity and inflammation in inflammatory bowel disease. *Curr Opin Gastroenterol.* 2006;22(4):361-364.
6. Podolsky DK. Inflammatory bowel disease (first of two parts). *N Engl J Med.* 1991;325(13):928-937.
7. Lee M, Chang EB. Inflammatory bowel diseases (IBD) and the microbiome—searching the crime scene for clues. *Gastroenterology.* 2021;160(2):524-537.
8. Wong JMW, de Souza R, Kendall CWC, Emam A, Jenkins DJA. Colonic health: fermentation and short chain fatty acids. *J Clin Gastroenterol.* 2006;40(3):235-243.
9. Sun MM, Wu W, Liu ZJ, Cong YZ. Microbiota metabolite short chain fatty acids, GPCR, and inflammatory bowel diseases. *J Gastroenterol.* 2017;52(1):1-8.
10. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. *Cell.* 2016;165(6):1332-1345.
11. Sun MM, Wu W, Chen L, et al. Microbiota-derived short-chain fatty acids promote Th1 cell IL-10 production to maintain intestinal homeostasis. *Nat Commun.* 2018;9(1):3555. https://doi.org/10.1038/s41467-018-05901-2.
12. Huda-Faujan N, Abdulamir AS, Fatimah AB, et al. The impact of the level of the intestinal short chain fatty acids in inflammatory bowel disease patients versus healthy subjects. *Open Biochem J.* 2010;4:53-58.
13. Machiels K, Joossens M, Sabino J, et al. A decrease of the butyrate-producing species *Roseburia hominis* and *Faecalibacterium prausnitzii* defines dysbiosis in patients with ulcerative colitis. *Gut.* 2014;63(8):1275-1283.
14. Vernia P, Monteleone G, Grandinetti G, et al. Combined oral sodium butyrate and mesalazine treatment compared to oral mesalazine alone in ulcerative colitis: randomized, double-blind, placebo-controlled pilot study. *Dig Dis Sci.* 2000;45(5):976-981.
15. Singh R, Chandrashekharappa S, Bodduluri SR, et al. Enhancement of the gut barrier integrity by a microbial metabolite through the Nrf2 pathway. *Nat Commun.* 2019;10(1):89. https://doi.org/10.1038/s41467-018-07859-7.
16. Sinha SR, Haileselassie Y, Nguyen LP, et al. Dysbiosis-induced secondary bile acid deficiency promotes intestinal inflammation. *Cell Host Microbe.* 2020;27(4):659-670.e5.
17. Lopez J, Grinspan A. Fecal microbiota transplantation for inflammatory bowel disease. *Gastroenterol Hepatol (N Y).* 2016;12(6):374-379.
18. Ye J, Erland LAE, Gill SK, et al. Metabolomics-guided hypothesis generation for mechanisms of intestinal protection by live biotherapeutic products. *Biomolecules.* 2021;11(5):738. https://doi.org/10.3390/biom11050738.
19. Markowiak-Kopeć P, Śliżewska K. The effect of probiotics on the production of short-chain fatty acids by human intestinal microbiome. *Nutrients.* 2020;12(4):1107. https://doi.org/10.3390/nu12041107.
20. Bamias G, Cominelli F. Immunopathogenesis of inflammatory bowel disease: current concepts. *Curr Opin Gastroenterol.* 2007;23(4):365-369.
21. Steinman L. A brief history of T_H17, the first major revision in the T_H1/T_H2 hypothesis of T cell–mediated tissue damage. *Nat Med.* 2007;13(2):139-145.
22. Langrish CL, Chen Y, Blumenschein WM, et al. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *J Exp Med.* 2005;201(2):233-240.
23. Yen D, Cheung J, Scheerens H, et al. IL-23 is essential for T cell–mediated colitis and promotes inflammation via IL-17 and IL-6. *J Clin Invest.* 2006;116(5):1310-1316.
24. Karampoor S, Zahednasab H, Farahmand M, et al. A possible pathogenic role of Syndecan-1 in the pathogenesis of coronavirus disease 2019 (COVID-19). *Int Immunopharmacol.* 2021;97:107684. https://doi.org/10.1016/j.intimp.2021.107684.
25. Kullberg MC, Jankovic D, Feng CG, et al. IL-23 plays a key role in *Helicobacter hepaticus*–induced T cell–dependent colitis. *J Exp Med.* 2006;203(11):2485-2494.
26. Zhang Z, Zheng M, Bindas J, Schwarzenberger P, Kolls JK. Critical role of IL-17 receptor signaling in acute TNBS-induced colitis. *Inflamm Bowel Dis.* 2006;12(5):382-388.
27. Andoh A, Ogawa A, Bamba S, Fujiyama Y. Interaction between interleukin-17-producing $CD4^+$ T cells and colonic subepithelial myofibroblasts: what are they doing in mucosal inflammation? *J Gastroenterol.* 2007;42(Suppl):29-33.
28. Fujino S, Andoh A, Bamba S, et al. Increased expression of interleukin 17 in inflammatory bowel disease. *Gut.* 2003;52(1):65-70.

29. Schmidt C, Giese T, Ludwig B, et al. Expression of interleukin-12-related cytokine transcripts in inflammatory bowel disease: elevated interleukin-23p19 and interleukin-27p28 in Crohn's disease but not in ulcerative colitis. _Inflamm Bowel Dis._ 2005;11(1):16-23.

30. Mannon PJ, Fuss IJ, Mayer L, et al; Anti–interleukin-12 antibody for active Crohn's disease. _N Engl J Med._ 2004;351(20):2069-2079.

31. Fuss IJ, Becker C, Yang Z, et al. Both IL-12p70 and IL-23 are synthesized during active Crohn's disease and are down-regulated by treatment with anti-IL-12 p40 monoclonal antibody. _Inflamm Bowel Dis._ 2006;12(1):9-15.

32. Duerr RH, Taylor KD, Brant SR, et al. A genome-wide association study identifies _IL23R_ as an inflammatory bowel disease gene. _Science._ 2006;314(5804):1461-1463.

33. Migone TS, Zhang J, Luo X, et al. TL1A is a TNF-like ligand for DR3 and TR6/DcR3 and functions as a T cell costimulator. _Immunity._ 2002;16(3):479-492.

34. Bamias G, Mishina M, Nyce M, et al. Role of TL1A and its receptor DR3 in two models of chronic murine ileitis. _Proc Natl Acad Sci U S A._ 2006;103(22):8441-8446.

35. Bamias C, Martin C 3rd, Marini M, et al. Expression, localization, and functional activity of TL1A, a novel Th1-polarizing cytokine in inflammatory bowel disease. _J Immunol._ 2003;171(9):4868-4874.

36. Prehn JL, Mehdizadeh S, Landers CJ, et al. Potential role for TL1A, the new TNF-family member and potent costimulator of IFN-γ, in mucosal inflammation. _Clin Immunol._ 2004;112(1):66-77.

37. Yamazaki K, McGovern D, Ragoussis J, et al. Single nucleotide polymorphisms in _TNFSF15_ confer susceptibility to Crohn's disease. _Hum Mol Genet._ 2005;14(22):3499-3506.

38. Mirzaei R, Dehkhodaie E, Bouzari B, et al. Dual role of microbiota-derived short-chain fatty acids on host and pathogen. _Biomed Pharmacother._ 2022;145:112352. https://doi.org/10.1016/j.biopha.2021.112352.

39. Almeida A, Mitchell AL, Boland M, et al. A new genomic blueprint of the human gut microbiota. _Nature._ 2019;568(7753):499-504.

40. Yoshimatsu Y, Mikami Y, Kanai T. Bacteriotherapy for inflammatory bowel disease. _Inflamm Regen._ 2021;41(1):3. https://doi.org/10.1186/s41232-020-00153-4.

41. Lee SH, Kwon JE, Cho ML. Immunological pathogenesis of inflammatory bowel disease. _Intest Res._ 2018;16(1):26-42.

42. Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. _Proc Natl Acad Sci U S A._ 2007;104(34):13780-13785.

43. Sokol H, Lay C, Seksik P, Tannock GW. Analysis of bacterial bowel communities of IBD patients: what has it revealed? _Inflamm Bowel Dis._ 2008;14(6):858-867.

44. Sokol H, Pigneur B, Watterlot L, et al. _Faecalibacterium prausnitzii_ is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. _Proc Natl Acad Sci U S A._ 2008;105(43):16731-16736.

45. Atarashi K, Tanoue T, Oshima K, et al. T$_{reg}$ induction by a rationally selected mixture of Clostridia strains from the human microbiota. _Nature._ 2013;500(7461):232-236.

46. Atarashi K, Tanoue T, Shima T, et al. Induction of colonic regulatory T cells by indigenous _Clostridium_ species. _Science._ 2011;331(6015):337-341.

47. Feller M, Huwiler K, Stephan R, et al. _Mycobacterium avium_ subspecies _paratuberculosis_ and Crohn's disease: a systematic review and meta-analysis. _Lancet Infect Dis._ 2007;7(9):607-613.

48. Selby W, Pavli P, Crotty B, et al; Antibiotics in Crohn's Disease Study Group. Two-year combination antibiotic therapy with clarithromycin, rifabutin, and clofazimine for Crohn's disease. _Gastroenterology._ 2007;132(7):2313-2319.

49. Chen W, Li D, Paulus B, Wilson I, Chadwick VS. Detection of _Listeria monocytogenes_ by polymerase chain reaction in intestinal mucosal biopsies from patients with inflammatory bowel disease and controls. _J Gastroenterol Hepatol._ 2000;15(10):1145-1150.

50. Clavijo GO, Salado CT, Carnerero EL, et al. _Listeria monocytogenes_ and its relationship with non-biological therapy in inflammatory bowel disease. _Gastroenterol Hepatol._ 2015;38(7):442-443. [in Spanish].

51. Rolhion N, Darfeuille-Michaud A. Adherent-invasive _Escherichia coli_ in inflammatory bowel disease. _Inflamm Bowel Dis._ 2007;13(10):1277-1283.

52. Ohkusa T, Sato N, Ogihara T, Morita K, Ogawa M, Okayasu I. _Fusobacterium varium_ localized in the colonic mucosa of patients with ulcerative colitis stimulates species-specific antibody. _J Gastroenterol Hepatol._ 2002;17(8):849-853.

53. Mizuno S, Ono K, Mikami Y, et al. 5-Aminosalicylic acid intolerance is associated with a risk of adverse clinical outcomes and dysbiosis in patients with ulcerative colitis. _Intest Res._ 2020;18(1):69-78.

54. Ananthakrishnan AN, Luo C, Yajnik V, et al. Gut microbiome function predicts response to anti-integrin biologic therapy in inflammatory bowel diseases. _Cell Host Microbe._ 2017;21(5):603-610.e3.

55. Sales-Campos H, Basso PJ, Alves VBF, et al. Classical and recent advances in the treatment of inflammatory bowel diseases. _Braz J Med Biol Res._ 2015;48(2):96-107.

56. Alipour M, Zaidi D, Valcheva R, et al. Mucosal barrier depletion and loss of bacterial diversity are primary abnormalities in paediatric ulcerative colitis. _J Crohns Colitis._ 2016;10(4):462-471.

57. Lewis JD, Chen EZ, Baldassano RN, et al. Inflammation, antibiotics, and diet as environmental stressors of the gut microbiome in pediatric Crohn's disease. _Cell Host Microbe._ 2015;18(4):489-500.

58. Li MF, Yang LJ, Mu CL, et al. Gut microbial metabolome in inflammatory bowel disease: from association to therapeutic perspectives. _Comput Struct Biotechnol J._ 2022;20:2402-2414.

59. Descamps HC, Herrmann B, Wiredu D, Thaiss CA. The path toward using microbial metabolites as therapies. _EBioMedicine._ 2019;44:747-754.

60. Lavelle A, Sokol H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. _Nat Rev Gastroenterol Hepatol._ 2020;17(4):223-237.

61. Marchesi JR, Holmes E, Khan F, et al. Rapid and noninvasive metabonomic characterization of inflammatory bowel disease. _J Proteome Res._ 2007;6(2):546-551.

62. Vernia P, Caprilli R, Latella G, Barbetti F, Magliocca FM, Cittadini M. Fecal lactate and ulcerative colitis. _Gastroenterology._ 1988;95(6):1564-1568.

63. Vernia P, Gnaedinger A, Hauck W, Breuer RI. Organic anions and the diarrhea of inflammatory bowel disease. _Dig Dis Sci._ 1988;33(11):1353-1358.

64. Takaishi H, Matsuki T, Nakazawa A, et al. Imbalance in intestinal microflora constitution could be involved in the pathogenesis of inflammatory bowel disease. _Int J Med Microbiol._ 2008;298(5–6):463-472.

65. Banfi D, Moro E, Bosi A, et al. Impact of microbial metabolites on microbiota–gut–brain axis in inflammatory bowel disease. _Int J Mol Sci._ 2021;22(4):1623. https://doi.org/10.3390/ijms22041623.

66. Baj A, Moro E, Bistoletti M, Orlandi V, Crema F, Giaroni C. Glutamatergic signaling along the microbiota-gut-brain axis. _Int J Mol Sci._ 2019;20(6):1482. https://doi.org/10.3390/ijms20061482.

67. Sinagra E, Utzeri E, Morreale GC, Fabbri C, Pace F, Anderloni A. Microbiota-gut-brain axis and its affect inflammatory bowel disease: pathophysiological concepts and insights for clinicians. _World J Clin Cases._ 2020;8(6):1013-1025.

68. Dong LN, Wang M, Guo J, Wang JP. Role of intestinal microbiota and metabolites in inflammatory bowel disease. *Chin Med J (Engl)*. 2019;132(13):1610-1614.

69. Donohoe DR, Garge N, Zhang X, et al. The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon. *Cell Metab*. 2011;13(5):517-526.

70. Corrêa-Oliveira R, Fachi JL, Vieira A, Sato FT, Vinolo MAR. Regulation of immune cell function by short-chain fatty acids. *Clin Transl Immunology*. 2016;5(4):e73. https://doi.org/10.1038/cti.2016.17.

71. Park J, Kim M, Kang SG, et al. Short-chain fatty acids induce both effector and regulatory T cells by suppression of histone deacetylases and regulation of the mTOR–S6K pathway. *Mucosal Immunol*. 2015;8(1):80-93.

72. Yan JB, Luo MM, Chen ZY, He BH. The function and role of the Th17/Treg cell balance in inflammatory bowel disease. *J Immunol Res*. 2020;2020:8813558. https://doi.org/10.1155/2020/8813558.

73. He X, Liang B, Gu N. Th17/Treg imbalance and atherosclerosis. *Dis Markers*. 2020;2020:8821029. https://doi.org/10.1155/2020/8821029.

74. Fasching P, Stradner M, Graninger W, Dejaco C, Fessler J. Therapeutic potential of targeting the Th17/Treg axis in autoimmune disorders. *Molecules*. 2017;22(1):134. https://doi.org/10.3390/molecules22010134.

75. Hartog A, Belle FN, Bastiaans J, et al. A potential role for regulatory T-cells in the amelioration of DSS induced colitis by dietary non-digestible polysaccharides. *J Nutr Biochem*. 2015;26(3):227-233.

76. Ichiyama K, Yoshida H, Wakabayashi Y, et al. Foxp3 inhibits RORγt-mediated *IL-17A* mRNA transcription through direct interaction with RORγt. *J Biol Chem*. 2008;283(25):17003-17008.

77. Yamamoto B, Suzuki Y, Yonezu T, et al. *Cha-Koji*, comprising green tea leaves fermented with *Aspergillus luchuensis var kawachii kitahara*, increases regulatory T cell production in mice and humans. *Biosci Biotechnol Biochem*. 2018;82(5):885-892.

78. Zhang ZL, Zhang H, Chen T, Shi L, Wang DR, Tang D. Regulatory role of short-chain fatty acids in inflammatory bowel disease. *Cell Commun Signal*. 2022;20(1):64. https://doi.org/10.1186/s12964-022-00869-5.

79. Kim M, Qie Y, Park J, Kim CH. Gut microbial metabolites fuel host antibody responses. *Cell Host Microbe*. 2016;20(2):202-214.

80. Wu W, Sun M, Chen F, et al. Microbiota metabolite short-chain fatty acid acetate promotes intestinal IgA response to microbiota which is mediated by GPR43. *Mucosal Immunol*. 2017;10(4):946-956.

81. Parada Venegas D, De la Fuente MK, Landskron G, et al. Short chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. *Front Immunol*. 2019;10:277. https://doi.org/10.3389/fimmu.2019.00277.

82. Kumari R, Ahuja V, Paul J. Fluctuations in butyrate-producing bacteria in ulcerative colitis patients of North India. *World J Gastroenterol*. 2013;19(22):3404-3414.

83. Takahashi K, Nishida A, Fujimoto T, et al. Reduced abundance of butyrate-producing bacteria species in the fecal microbial community in Crohn's disease. *Digestion*. 2016;93(1):59-65.

84. Scheppach W, Sommer H, Kirchner T, et al. Effect of butyrate enemas on the colonic mucosa in distal ulcerative colitis. *Gastroenterology*. 1992;103(1):51-56.

85. Vernia P, Marcheggiano A, Caprilli R, et al. Short-chain fatty acid topical treatment in distal ulcerative colitis. *Aliment Pharmacol Ther*. 1995;9(3):309-313.

86. Di Sabatino A, Morera R, Ciccocioppo R, et al. Oral butyrate for mildly to moderately active Crohn's disease. *Aliment Pharmacol Ther*. 2005;22(9):789-794.

87. Lee JG, Lee J, Lee AR, et al. Impact of short-chain fatty acid supplementation on gut inflammation and microbiota composition in a murine colitis model. *J Nutr Biochem*. 2022;101:108926. https://doi.org/10.1016/j.jnutbio.2021.108926.

88. Lührs H, Gerke T, Müller JG, et al. Butyrate inhibits NF-κB activation in lamina propria macrophages of patients with ulcerative colitis. *Scand J Gastroenterol*. 2002;37(4):458-466.

89. Hamer HM, Jonkers D, Venema K, Vanhoutvin S, Troost FJ, Brummer RJ. Review article: the role of butyrate on colonic function. *Aliment Pharmacol Ther*. 2008;27(2):104-119.

90. Harig JM, Soergel KH, Komorowski RA, Wood CM. Treatment of diversion colitis with short-chain-fatty-acid irrigation. *N Engl J Med*. 1989;320(1):23-28.

91. Breuer RI, Soergel KH, Lashner BA, et al. Short chain fatty acid rectal irrigation for left-sided ulcerative colitis: a randomised, placebo controlled trial. *Gut*. 1997;40(4):485-491.

92. Hamer HM, Jonkers DMAE, Vanhoutvin SALW, et al. Effect of butyrate enemas on inflammation and antioxidant status in the colonic mucosa of patients with ulcerative colitis in remission. *Clin Nutr*. 2010;29(6):738-744.

93. Guillemot F, Colombel JF, Neut C, et al. Treatment of diversion colitis by short-chain fatty acids. Prospective and double-blind study. *Dis Colon Rectum*. 1991;34(10):861-864.

94. Tarrerias AL, Millecamps M, Alloui A, et al. Short-chain fatty acid enemas fail to decrease colonic hypersensitivity and inflammation in TNBS-induced colonic inflammation in rats. *Pain*. 2002;100(1–2):91-97.

95. Ji J, Shu DM, Zheng MZ, et al. Microbial metabolite butyrate facilitates M2 macrophage polarization and function. *Sci Rep*. 2016;6:24838. https://doi.org/10.1038/srep24838.

96. Chang PV, Hao L, Offermanns S, Medzhitov R. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. *Proc Natl Acad Sci U S A*. 2014;111(6):2247-2252.

97. Araki Y, Andoh A, Takizawa J, Takizawa W, Fujiyama Y. *Clostridium butyricum*, a probiotic derivative, suppresses dextran sulfate sodium-induced experimental colitis in rats. *Int J Mol Med*. 2004;13(4):577-580.

98. Boesmans L, Valles-Colomer M, Wang J, et al. Butyrate producers as potential next-generation probiotics: safety assessment of the administration of *Butyricicoccus pullicaecorum* to healthy volunteers. *mSystems*. 2018;3(6):e00094-18. https://doi.org/10.1128/mSystems.00094-18.

99. Magnusson MK, Isaksson S, Öhman L. The anti-inflammatory immune regulation induced by butyrate is impaired in inflamed intestinal mucosa from patients with ulcerative colitis. *Inflammation*. 2020;43(2):507-517.

100. Ferrer-Picón E, Dotti I, Corraliza AM, et al. Intestinal inflammation modulates the epithelial response to butyrate in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2020;26(1):43-55.

101. Jaworska K, Konop M, Bielinska K, et al. Inflammatory bowel disease is associated with increased gut-to-blood penetration of short-chain fatty acids: a new, non-invasive marker of a functional intestinal lesion. *Exp Physiol*. 2019;104(8):1226-1236.

102. Abdelazeem KNM, Kalo MZ, Beer-Hammer S, Lang F. The gut microbiota metabolite urolithin A inhibits NF-κB activation in LPS stimulated BMDMs. *Sci Rep*. 2021;11(1):7117. https://doi.org/10.1038/s41598-021-86514-6.

103. Cásedas G, Les F, Choya-Foces C, Hugo M, López V. The metabolite urolithin-A ameliorates oxidative stress in Neuro-2a cells, becoming a potential neuroprotective agent. *Antioxidants (Basel)*. 2020;9(2):177. https://doi.org/10.3390/antiox9020177.

104. Larrosa M, González-Sarrías A, García-Conesa MT, Tomás-Barberán FA, Espín JC. Urolithins, ellagic acid-derived metabolites produced by human colonic microflora, exhibit estrogenic and anti-estrogenic activities. *J Agric Food Chem*. 2006;54(5):1611-1620.

105. Tomás-Barberán FA, García-Villalba R, González-Sarrías A, Selma MV, Espín JC. Ellagic acid metabolism by human gut

microbiota: consistent observation of three urolithin phenotypes in intervention trials, independent of food source, age, and health status. *J Agric Food Chem*. 2014;62(28):6535-6538.

106. Sánchez-González C, Ciudad CJ, Izquierdo-Pulido M, Noé V. Urolithin A causes p21 up-regulation in prostate cancer cells. *Eur J Nutr*. 2016;55(3):1099-1112.

107. Koch W. Dietary polyphenols—important non-nutrients in the prevention of chronic noncommunicable diseases. A systematic review. *Nutrients*. 2019;11(5):1039. https://doi.org/10.3390/nu1105 1039.

108. Espín JC, Larrosa M, García-Conesa MT, Tomás-Barberán F. Biological significance of urolithins, the gut microbial ellagic acid-derived metabolites: the evidence so far. *Evid Based Complement Alternat Med*. 2013;2013:270418. https://doi.org/10.1155/2013/270418.

109. Gong Z, Huang JY, Xu B, et al. Urolithin A attenuates memory impairment and neuroinflammation in APP/PS1 mice. *J Neuroinflammation*. 2019;16(1):62. https://doi.org/10.1186/s12974-019-1450-3.

110. Kim KB, Lee S, Kim JH. Neuroprotective effects of urolithin A on H_2O_2-induced oxidative stress-mediated apoptosis in SK-N-MC cells. *Nutr Res Pract*. 2020;14(1):3-11.

111. Kujawska M, Jourdes M, Kurpik M, et al. Neuroprotective effects of pomegranate juice against Parkinson's disease and presence of ellagitannins-derived metabolite—urolithin A—in the brain. *Int J Mol Sci*. 2020;21(1):202. https://doi.org/10.3390/ijms21010202.

112. Lee G, Park JS, Lee EJ, Ahn JH, Kim HS. Anti-inflammatory and anti-oxidant mechanisms of urolithin B in activated microglia. *Phytomedicine*. 2019;55:50-57.

113. Selma MV, Beltrán D, García-Villalba R, Espín JC, Tomás-Barberán FA. Description of urolithin production capacity from ellagic acid of two human intestinal *Gordonibacter* species. *Food Funct*. 2014;5(8):1779-1784.

114. Ding SL, Pang ZY, Chen XM, et al. Urolithin A attenuates IL-1β-induced inflammatory responses and cartilage degradation via inhibiting the MAPK/NF-κB signaling pathways in rat articular chondrocytes. *J Inflamm (Lond)*. 2020;17:13. https://doi.org/10.1186/s12950-020-00242-8.

115. Larrosa M, González-Sarrías A, Yáñez-Gascón MJ, et al. Anti-inflammatory properties of a pomegranate extract and its metabolite urolithin-A in a colitis rat model and the effect of colon inflammation on phenolic metabolism. *J Nutr Biochem*. 2010;21(8):717-725.

116. Zhang SQ, Al-Maghout T, Cao H, et al. Gut bacterial metabolite urolithin A (UA) mitigates Ca^{2+} entry in T cells by regulating miR-10a-5p. *Front Immunol*. 2019;10:1737. https://doi.org/10.3389/fimmu.2019.01737.

117. Gadaleta RM, van Mil SWC, Oldenburg B, Siersema PD, Klomp LWJ, van Erpecum KJ. Bile acids and their nuclear receptor FXR: relevance for hepatobiliary and gastrointestinal disease. *Biochim Biophys Acta*. 2010;1801(7):683-692.

118. Philipp B. Bacterial degradation of bile salts. *Appl Microbiol Biotechnol*. 2011;89(4):903-915.

119. Jasim SA, Kzar HH, Hamad MH, et al. The emerging role of 27-hydroxycholesterol in cancer development and progression: an update. *Int Immunopharmacol*. 2022;110:109074. https://doi.org/10.1016/j.intimp.2022.109074.

120. Claudel T, Staels B, Kuipers F. The Farnesoid X receptor: a molecular link between bile acid and lipid and glucose metabolism. *Arterioscler Thromb Vasc Biol*. 2005;25(10):2020-2030.

121. Matsubara T, Li F, Gonzalez FJ. FXR signaling in the enterohepatic system. *Mol Cell Endocrinol*. 2013;368(1–2):17-29.

122. Tiratterra E, Franco P, Porru E, Katsanos KH, Christodoulou DK, Roda G. Role of bile acids in inflammatory bowel disease. *Ann Gastroenterol*. 2018;31(3):266-272.

123. Vítek L. Bile acid malabsorption in inflammatory bowel disease. *Inflamm Bowel Dis*. 2015;21(2):476-483.

124. Sun RC, Xu CJ, Feng BS, Gao X, Liu ZJ. Critical roles of bile acids in regulating intestinal mucosal immune responses. *Therap Adv Gastroenterol*. 2021;14:17562848211018098. https://doi.org/10.1177/17562848211018098.

125. Hold GL, Smith M, Grange C, Watt ER, El-Omar EM, Mukhopadhya I. Role of the gut microbiota in inflammatory bowel disease pathogenesis: what have we learnt in the past 10 years? *World J Gastroenterol*. 2014;20(5):1192-1210.

126. Mattar MC, Lough D, Pishvaian MJ, Charabaty A. Current management of inflammatory bowel disease and colorectal cancer. *Gastrointest Cancer Res*. 2011;4(2):53-61.

127. Mirzaei R, Sabokroo N, Ahmadyousefi Y, Motamedi H, Karampoor S. Immunometabolism in biofilm infection: lessons from cancer. *Mol Med*. 2022;28(1):10. https://doi.org/10.1186/s10020-022-00435-2.

128. Morelli L, Capurso L. FAO/WHO guidelines on probiotics: 10 years later. *J Clin Gastroenterol*. 2012;46(Suppl):S1-S2.

129. Louis P, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. *Nat Rev Microbiol*. 2014;12(10):661-672.

130. Mirzaei R, Attar A, Papizadeh S, et al. The emerging role of probiotics as a mitigation strategy against coronavirus disease 2019 (COVID-19). *Arch Virol*. 2021;166(7):1819-1840.

131. Travers MA, Sow C, Zirah S, et al. Deconjugated bile salts produced by extracellular bile-salt hydrolase-like activities from the probiotic *Lactobacillus johnsonii* La1 inhibit *Giardia duodenalis in vitro* growth. *Front Microbiol*. 2016;7:1453. https://doi.org/10.3389/fmicb.2016.01453.

132. Buffie CG, Bucci V, Stein RR, et al. Precision microbiome reconstitution restores bile acid mediated resistance to *Clostridium difficile*. *Nature*. 2015;517(7533):205-208.

133. Inagaki T, Moschetta A, Lee YK, et al. Regulation of antibacterial defense in the small intestine by the nuclear bile acid receptor. *Proc Natl Acad Sci U S A*. 2006;103(10):3920-3925.

134. Verbeke L, Farre R, Verbinnen B, et al. The FXR agonist obeticholic acid prevents gut barrier dysfunction and bacterial translocation in cholestatic rats. *Am J Pathol*. 2015;185(2):409-419.

135. Crawley ML. Farnesoid X receptor modulators: a patent review. *Expert Opin Ther Pat*. 2010;20(8):1047-1057.

136. Bahar R, Wong KA, Liu CH, Bowlus CL. Update on new drugs and those in development for the treatment of primary biliary cholangitis. *Gastroenterol Hepatol (N Y)*. 2018;14(3):154-163.

137. Massafra V, Pellicciari R, Gioiello A, van Mil SWC. Progress and challenges of selective farnesoid X receptor modulation. *Pharmacol Ther*. 2018;191:162-177.

138. Van den Bossche L, Borsboom D, Devriese S, et al. Tauroursodeoxycholic acid protects bile acid homeostasis under inflammatory conditions and dampens Crohn's disease-like ileitis. *Lab Invest*. 2017;97(5):519-529.

139. Merlen G, Kahale N, Ursic-Bedoya J, et al. TGR5-dependent hepatoprotection through the regulation of biliary epithelium barrier function. *Gut*. 2020;69(1):146-157.

140. Sorrentino G, Perino A, Yildiz E, et al. Bile acids signal via TGR5 to activate intestinal stem cells and epithelial regeneration. *Gastroenterology*. 2020;159(3):956-968.e8.

141. Fiorucci S, Biagioli M, Zampella A, Distrutti E. Bile acids activated receptors regulate innate immunity. *Front Immunol*. 2018;9:1853. https://doi.org/10.3389/fimmu.2018.01853.

142. Perides G, Laukkarinen JM, Vassileva G, Steer ML. Biliary acute pancreatitis in mice is mediated by the G-protein–coupled cell surface bile acid receptor Gpbar1. *Gastroenterology*. 2010;138(2):715-725.

143. Bunnett NW. Neuro-humoral signalling by bile acids and the TGR5 receptor in the gastrointestinal tract. *J Physiol*. 2014;592(14):2943-2950.

144. Kawamata Y, Fujii R, Hosoya M, et al. A G protein-coupled receptor responsive to bile acids. *J Biol Chem*. 2003;278(11):9435-9440.

145. Yoneno K, Hisamatsu T, Shimamura K, et al. TGR5 signalling inhibits the production of pro-inflammatory cytokines by *in vitro* differentiated inflammatory and intestinal macrophages in Crohn's disease. *Immunology*. 2013;139(1):19-29.

146. Hov JR, Keitel V, Schrumpf E, Häussinger D, Karlsen TH. TGR5 sequence variation in primary sclerosing cholangitis. *Dig Dis*. 2011;29(1):78-84.

147. Pols TWH, Nomura M, Harach T, et al. TGR5 activation inhibits atherosclerosis by reducing macrophage inflammation and lipid loading. *Cell Metab*. 2011;14(6):747-757.

148. Wang YD, Chen WD, Yu DN, Forman BM, Huang WD. The G-protein-coupled bile acid receptor, Gpbar1 (TGR5), negatively regulates hepatic inflammatory response through antagonizing nuclear factor κ light-chain enhancer of activated B cells (NF-κB) in mice. *Hepatology*. 2011;54(4):1421-1432.

149. Venkatesh M, Mukherjee S, Wang H, et al. Symbiotic bacterial metabolites regulate gastrointestinal barrier function via the xenobiotic sensor PXR and Toll-like receptor 4. *Immunity*. 2014;41(2):296-310.

150. Zhou C, Tabb MM, Nelson EL, et al. Mutual repression between steroid and xenobiotic receptor and NF-κB signaling pathways links xenobiotic metabolism and inflammation. *J Clin Invest*. 2006;116(8):2280-2289.

151. Wang S, Martins R, Sullivan MC, et al. Diet-induced remission in chronic enteropathy is associated with altered microbial community structure and synthesis of secondary bile acids. *Microbiome*. 2019;7(1):126. https://doi.org/10.1186/s40168-019-0740-4.

152. Ke J, Li Y, Han CQ, et al. Fucose ameliorate intestinal inflammation through modulating the crosstalk between bile acids and gut microbiota in a chronic colitis murine model. *Inflamm Bowel Dis*. 2020;26(6):863-873.

153. Jia YQ, Yuan ZW, Zhang XS, et al. Total alkaloids of *Sophora alopecuroides* L. ameliorated murine colitis by regulating bile acid metabolism and gut microbiota. *J Ethnopharmacol*. 2020;255:112775. https://doi.org/10.1016/j.jep.2020.112775.

154. Diederen K, Li JV, Donachie GE, et al. Exclusive enteral nutrition mediates gut microbial and metabolic changes that are associated with remission in children with Crohn's disease. *Sci Rep*. 2020;10(1):18879. https://doi.org/10.1038/s41598-020-75306-z.

155. Tsertsvadze A, Gurung T, Court R, Clarke A, Sutcliffe P. Clinical effectiveness and cost-effectiveness of elemental nutrition for the maintenance of remission in Crohn's disease: a systematic review and meta-analysis. *Health Technol Assess*. 2015;19(26):1-138.

156. Duboc H, Rajca S, Rainteau D, et al. Connecting dysbiosis, bile-acid dysmetabolism and gut inflammation in inflammatory bowel diseases. *Gut*. 2013;62(4):531-539.

157. Wohlgemuth S, Keller S, Kertscher R, et al. Intestinal steroid profiles and microbiota composition in colitic mice. *Gut Microbes*. 2011;2(3):159-166.

158. Devkota S, Wang Y, Musch MW, et al. Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in *Il10*$^{-/-}$ mice. *Nature*. 2012;487(7405):104-108.

159. Ridlon JM, Wolf PG, Gaskins HR. Taurocholic acid metabolism by gut microbes and colon cancer. *Gut Microbes*. 2016;7(3):201-215.

160. Magee EA, Richardson CJ, Hughes R, Cummings JH. Contribution of dietary protein to sulfide production in the large intestine: an in vitro and a controlled feeding study in humans. *Am J Clin Nutr*. 2000;72(6):1488-1494.

161. Gadaleta RM, van Erpecum KJ, Oldenburg B, et al. Farnesoid X receptor activation inhibits inflammation and preserves the intestinal barrier in inflammatory bowel disease. *Gut*. 2011;60(4):463-472.

162. Attinkara R, Mwinyi J, Truninger K, et al; Swiss IBD Cohort Study Group. Association of genetic variation in the *NR1H4* gene, encoding the nuclear bile acid receptor FXR, with inflammatory bowel disease. *BMC Res Notes*. 2012;5:461. https://doi.org/10.1186/1756-0500-5-461.

163. Vaughn BP, Kaiser T, Staley C, et al. A pilot study of fecal bile acid and microbiota profiles in inflammatory bowel disease and primary sclerosing cholangitis. *Clin Exp Gastroenterol*. 2019;12:9-19.

164. Hou RG, Fan L, Liu JJ, et al. Bile acid malabsorption is associated with diarrhea in acute phase of colitis. *Can J Physiol Pharmacol*. 2018;96(12):1328-1336.

165. Mena Bares LM, Benítez Cantero JM, Iglesias Flores E, et al. Bile acid malabsorption in patients with chronic diarrhea and Crohn's disease. *Rev Esp Enferm Dig*. 2019;111(1):40-45.

166. Martoni CJ, Labbé A, Ganopolsky JG, Prakash S, Jones ML. Changes in bile acids, FGF-19 and sterol absorption in response to bile salt hydrolase active *L. reuteri* NCIMB 30242. *Gut Microbes*. 2015;6(1):57-65.

167. Zhai QX, Liu Y, Wang C, et al. *Lactobacillus plantarum* CCFM8661 modulates bile acid enterohepatic circulation and increases lead excretion in mice. *Food Funct*. 2019;10(3):1455-1464.

168. Degirolamo C, Rainaldi S, Bovenga F, Murzilli S, Moschetta A. Microbiota modification with probiotics induces hepatic bile acid synthesis via downregulation of the Fxr-Fgf15 axis in mice. *Cell Rep*. 2014;7(1):12-18.

169. Vandeputte D, Falony G, Vieira-Silva S, et al. Prebiotic inulin-type fructans induce specific changes in the human gut microbiota. *Gut*. 2017;66(11):1968-1974.

170. Scott KP, Martin JC, Duncan SH, Flint HJ. Prebiotic stimulation of human colonic butyrate-producing bacteria and bifidobacteria, in vitro. *FEMS Microbiol Ecol*. 2014;87(1):30-40.

171. Valcheva R, Koleva P, Martínez I, Walter J, Gänzle MG, Dieleman LA. Inulin-type fructans improve active ulcerative colitis associated with microbiota changes and increased short-chain fatty acids levels. *Gut Microbes*. 2019;10(3):334-357.

172. Alexander C, Cross TWL, Devendran S, et al. Effects of prebiotic inulin-type fructans on blood metabolite and hormone concentrations and faecal microbiota and metabolites in overweight dogs. *Br J Nutr*. 2018;120(6):711-720.

173. Keely SJ, Steer CJ, Lajczak-McGinley NK. Ursodeoxycholic acid: a promising therapeutic target for inflammatory bowel diseases? *Am J Physiol Gastrointest Liver Physiol*. 2019;317(6):G872-G881.

174. Kullmann F, Arndt H, Gross V, Rüschoff J, Schölmerich J. Beneficial effect of ursodeoxycholic acid on mucosal damage in trinitrobenzene sulphonic acid-induced colitis. *Eur J Gastroenterol Hepatol*. 1997;9(12):1205-1211.

175. Kullmann F, Gross V, Rüschoff J, et al. Effect of ursodeoxycholic acid on the inflammatory activity of indomethacin-induced intestinal inflammation in rats. *Z Gastroenterol*. 1997;35(3):171-178.

176. Wang WJ, Zhao JF, Gui WF, et al. Tauroursodeoxycholic acid inhibits intestinal inflammation and barrier disruption in mice with non-alcoholic fatty liver disease. *Br J Pharmacol*. 2018;175(3):469-484.

177. Paramsothy S, Paramsothy R, Rubin DT, et al. Faecal microbiota transplantation for inflammatory bowel disease: a systematic review and meta-analysis. *J Crohns Colitis*. 2017;11(10):1180-1199.

178. Moayyedi P, Surette MG, Kim PT, et al. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. *Gastroenterology*. 2015;149(1):102-109.e6.

179. Paramsothy S, Kamm MA, Kaakoush NO, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. *Lancet*. 2017;389(10075):1218-1228.

180. Rossen NG, Fuentes S, van der Spek MJ, et al. Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis. *Gastroenterology*. 2015;149(1):110-118.e4.

181. Vaughn BP, Vatanen T, Allegretti JR, et al. Increased intestinal microbial diversity following fecal microbiota transplant for active Crohn's disease. *Inflamm Bowel Dis*. 2016;22(9):2182-2190.

182. Cui BT, Feng Q, Wang HG, et al. Fecal microbiota transplantation through mid-gut for refractory Crohn's disease: safety, feasibility, and efficacy trial results. *J Gastroenterol Hepatol*. 2015;30(1):51-58.

183. Suskind DL, Brittnacher MJ, Wahbeh G, et al. Fecal microbial transplant effect on clinical outcomes and fecal microbiome in active Crohn's disease. *Inflamm Bowel Dis*. 2015;21(3):556-563.

184. Colman RJ, Rubin DT. Fecal microbiota transplantation as therapy for inflammatory bowel disease: a systematic review and meta-analysis. *J Crohns Colitis*. 2014;8(12):1569-1581.

185. De Leon LM, Watson JB, Kelly CR. Transient flare of ulcerative colitis after fecal microbiota transplantation for recurrent *Clostridium difficile* infection. *Clin Gastroenterol Hepatol*. 2013;11(8):1036-1038.

186. Kelly CR, Ihunnah C, Fischer M, et al. Fecal microbiota transplant for treatment of *Clostridium difficile* infection in immunocompromised patients. *Am J Gastroenterol*. 2014;109(7):1065-1071.

187. Reid G. Safe and efficacious probiotics: what are they? *Trends Microbiol*. 2006;14(8):348-352.

188. Isaacs K, Herfarth H. Role of probiotic therapy in IBD. *Inflamm Bowel Dis*. 2008;14(11):1597-1605.

189. Zuo T, Ng SC. The gut microbiota in the pathogenesis and therapeutics of inflammatory bowel disease. *Front Microbiol*. 2018;9:2247. https://doi.org/10.3389/fmicb.2018.02247.

190. Basso PJ, Câmara NOS, Sales-Campos H. Microbial-based therapies in the treatment of inflammatory bowel disease — an overview of human studies. *Front Pharmacol*. 2019;9:1571. https://doi.org/10.3389/fphar.2018.01571.

191. Tursi A, Brandimarte G, Papa A, et al. Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic VSL#3 as adjunctive to a standard pharmaceutical treatment: a double-blind, randomized, placebo-controlled study. *Am J Gastroenterol*. 2010;105(10):2218-2227.

192. Mardini HE, Grigorian AY. Probiotic mix VSL#3 is effective adjunctive therapy for mild to moderately active ulcerative colitis: a meta-analysis. *Inflamm Bowel Dis*. 2014;20(9):1562-1567.

193. Sood A, Midha V, Makharia GK, et al. The probiotic preparation, VSL#3 induces remission in patients with mild-to-moderately active ulcerative colitis. *Clin Gastroenterol Hepatol*. 2009;7(11):1202-1209.e1.

194. Kruis W, Fric P, Pokrotnieks J, et al. Maintaining remission of ulcerative colitis with the probiotic *Escherichia coli* Nissle 1917 is as effective as with standard mesalazine. *Gut*. 2004;53(11):1617-1623.

195. Kato K, Mizuno S, Umesaki Y, et al. Randomized placebo-controlled trial assessing the effect of bifidobacteria-fermented milk on active ulcerative colitis. *Aliment Pharmacol Ther*. 2004;20(10):1133-1141.

196. Matsuoka K, Uemura Y, Kanai T, et al. Efficacy of *Bifidobacterium breve* fermented milk in maintaining remission of ulcerative colitis. *Dig Dis Sci*. 2018;63(7):1910-1919.

197. Gargari G, Taverniti V, Balzaretti S, et al. Consumption of a *Bifidobacterium bifidum* strain for 4 weeks modulates dominant intestinal bacterial taxa and fecal butyrate in healthy adults. *Appl Environ Microbiol*. 2016;82(19):5850-5859.

198. Zocco MA, dal Verme LZ, Cremonini F, et al. Efficacy of *Lactobacillus* GG in maintaining remission of ulcerative colitis. *Aliment Pharmacol Ther*. 2006;23(11):1567-1574.

199. Martín R, Chain F, Miquel S, et al. Using murine colitis models to analyze probiotics–host interactions. *FEMS Microbiol Rev*. 2017;41(Suppl):S49-S70.

200. Foligne B, Nutten S, Grangette C, et al. Correlation between *in vitro* and *in vivo* immunomodulatory properties of lactic acid bacteria. *World J Gastroenterol*. 2007;13(2):236-243.

201. Maeda S, Ohno K, Nakamura K, et al. Mucosal imbalance of interleukin-1β and interleukin-1 receptor antagonist in canine inflammatory bowel disease. *Vet J*. 2012;194(1):66-70.

202. Nishitani Y, Tanoue T, Yamada K, et al. *Lactococcus lactis* subsp. *cremoris* FC alleviates symptoms of colitis induced by dextran sulfate sodium in mice. *Int Immunopharmacol*. 2009;9(12):1444-1451.

203. Bekkers M, Stojkovic B, Kaiko GE. Mining the microbiome and microbiota-derived molecules in inflammatory bowel disease. *Int J Mol Sci*. 2021;22(20):11243. https://doi.org/10.3390/ijms222011243.

204. Kaiko GE, Stappenbeck TS. Host–microbe interactions shaping the gastrointestinal environment. *Trends Immunol*. 2014;35(11):538-548.

205. Donaldson GP, Lee SM, Mazmanian SK. Gut biogeography of the bacterial microbiota. *Nat Rev Microbiol*. 2016;14(1):20-32.

206. Ruff WE, Greiling TM, Kriegel MA. Host–microbiota interactions in immune-mediated diseases. *Nat Rev Microbiol*. 2020;18(9):521-538.

207. Guo CJ, Allen BM, Hiam KJ, et al. Depletion of microbiome-derived molecules in the host using *Clostridium* genetics. *Science*. 2019;366(6471):eaav1282. https://doi.org/10.1126/science.aav1282.

208. Mazmanian SK, Round JL, Kasper DL. A microbial symbiosis factor prevents intestinal inflammatory disease. *Nature*. 2008;453(7195):620-625.

209. Atarashi K, Tanoue T, Ando M, et al. Th17 cell induction by adhesion of microbes to intestinal epithelial cells. *Cell*. 2015;163(2):367-380.

210. Viladomiu M, Kivolowitz C, Abdulhamid A, et al. IgA-coated *E. coli* enriched in Crohn's disease spondyloarthritis promote T$_H$17-dependent inflammation. *Sci Transl Med*. 2017;9(376):eaaf9665. https://doi.org/10.1126/scitranslmed.aaf9655.

211. Mishima Y, Sartor RB. Manipulating resident microbiota to enhance regulatory immune function to treat inflammatory bowel diseases. *J Gastroenterol*. 2020;55(1):4-14.

212. Charbonneau MR, Isabella VM, Li N, Kurtz CB. Developing a new class of engineered live bacterial therapeutics to treat human diseases. *Nat Commun*. 2020;11(1):1738. https://doi.org/10.1038/s41467-020-15508-1.

213. Ross JJ, Boucher PE, Bhattacharyya SP, et al. Considerations in the development of live biotherapeutic products for clinical use. *Curr Issues Mol Biol*. 2008;10(1–2):13-16.

214. Claesen J, Fischbach MA. Synthetic microbes as drug delivery systems. *ACS Synth Biol*. 2015;4(4):358-364.

215. Schultz M. Clinical use of *E. coli* Nissle 1917 in inflammatory bowel disease. *Inflamm Bowel Dis*. 2008;14(7):1012-1018.

216. Dignass A, Lindsay JO, Sturm A, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis*. 2012;6(10):991-1030.

217. Losurdo G, Iannone A, Contaldo A, Ierardi E, Di Leo A, Principi M. *Escherichia coli Nissle* 1917 in ulcerative colitis treatment: systematic review and meta-analysis. *J Gastrointestin Liver Dis*. 2015;24(4):499-505.

218. Praveschotinunt P, Duraj-Thatte AM, Gelfat I, Bahl F, Chou DB, Joshi NS. Engineered *E. coli* Nissle 1917 for the delivery of matrix-tethered therapeutic domains to the gut. *Nat Commun*. 2019;10(1):5580. https://doi.org/10.1038/s41467-019-13336-6.

219. Prantera C, Scribano ML, Falasco G, Andreoli A, Luzi C. Ineffectiveness of probiotics in preventing recurrence after curative resection for Crohn's disease: a randomised controlled trial with *Lactobacillus* GG. *Gut*. 2002;51(3):405-409.

220. Cui HH, Chen CL, Wang JD, et al. Effects of probiotic on intestinal mucosa of patients with ulcerative colitis. *World J Gastroenterol*. 2004;10(10):1521-1525.

221. 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(3):465-473.

222. Sang LX, Chang B, Zhang WL, Wu XM, Li XH, Jiang M. Remission induction and maintenance effect of probiotics on ulcerative colitis: a meta-analysis. *World J Gastroenterol*. 2010;16(15):1908-1915.

223. Misra B, Curran J, Herfarth H, et al. SER-287, an investigational microbiome therapeutic, induces remission and endoscopic improvement in a placebo-controlled, double-blind randomised trial

in patients with active mild-to-moderate ulcerative colitis. *J Crohns Colitis*. 2018;12(Suppl):S317.

224. Wrzosek L, Miquel S, Noordine M-L, et al. *Bacteroides thetaiotaomicron* and *Faecalibacterium prausnitzii* influence the production of mucus glycans and the development of goblet cells in the colonic epithelium of a gnotobiotic model rodent. *BMC Biol*. 2013;11:61. https://doi.org/10.1186/1741-7007-11-61.

225. Dreher-Lesnick SM, Stibitz S, Carlson PE Jr. U.S. regulatory considerations for development of live biotherapeutic products as drugs. *Microbiol Spectr*. 2017;5(5). https://doi.org/10.1128/microbiolspec.BAD-0017-2017.

226. Cohen LJ, Cho JH, Gevers D, Chu H. Genetic factors and the intestinal microbiome guide development of microbe-based therapies for inflammatory bowel diseases. *Gastroenterology*. 2019;156(8):2174-2189.

227. Smillie CS, Sauk J, Gevers D, et al. Strain tracking reveals the determinants of bacterial engraftment in the human gut following fecal microbiota transplantation. *Cell Host Microbe*. 2018;23(2):229-240.e5.

228. Maronek M, Link R, Ambro L, Gardlik R. Phages and their role in gastrointestinal disease: focus on inflammatory bowel disease. *Cell*. 2020;9(4):1013. https://doi.org/10.3390/cells9041013.

229. Summers WC. Bacteriophage therapy. *Annu Rev Microbiol*. 2001;55:437-451.

230. Międzybrodzki R, Borysowski J, Weber-Dąbrowska B, et al. Clinical aspects of phage therapy. *Adv Virus Res*. 2012;83:73-121.

231. Moelling K, Broecker F, Willy C. A wake-up call: we need phage therapy now. *Viruses*. 2018;10(12):688. https://doi.org/10.3390/v10120688.

232. Łusiak-Szelachowska M, Zaczek M, Weber-Dąbrowska B, et al. Phage neutralization by sera of patients receiving phage therapy. *Viral Immunol*. 2014;27(6):295-304.

233. Żaczek M, Łusiak-Szelachowska M, Jończyk-Matysiak E, et al. Antibody production in response to staphylococcal MS-1 phage cocktail in patients undergoing phage therapy. *Front Microbiol*. 2016;7:1681. https://doi.org/10.3389/fmicb.2016.01681.

234. Gogokhia L, Buhrke K, Bell R, et al. Expansion of bacteriophages is linked to aggravated intestinal inflammation and colitis. *Cell Host Microbe*. 2019;25(2):285-299.e8.

235. Miedzybrodzki R, Switala-Jelen K, Fortuna W, et al. Bacteriophage preparation inhibition of reactive oxygen species generation by endotoxin-stimulated polymorphonuclear leukocytes. *Virus Res*. 2008;131(2):233-242.

236. Górski A, Kniotek M, Perkowska-Ptasińska A, et al. Bacteriophages and transplantation tolerance. *Transplant Proc*. 2006;38(1):331-333.

237. Zhang LL, Hou X, Sun LC, et al. *Staphylococcus aureus* bacteriophage suppresses LPS-induced inflammation in MAC-T bovine mammary epithelial cells. *Front Microbiol*. 2018;9:1614. https://doi.org/10.3389/fmicb.2018.01614.

238. Górski A, Bollyky PL, Przybylski M, et al. Perspectives of phage therapy in non-bacterial infections. *Front Microbiol*. 2019;9:3306. https://doi.org/10.3389/fmicb.2018.03306.

239. Duerkop BA, Hooper LV. Resident viruses and their interactions with the immune system. *Nat Immunol*. 2013;14(7):654-659.

240. Norman JM, Handley SA, Baldridge MT, et al. Disease-specific alterations in the enteric virome in inflammatory bowel disease. *Cell*. 2015;160(3):447-460.

241. Cieplak T, Soffer N, Sulakvelidze A, Nielsen DS. A bacteriophage cocktail targeting *Escherichia coli* reduces *E. coli* in simulated gut conditions, while preserving a non-targeted representative commensal normal microbiota. *Gut Microbes*. 2018;9(5):391-399.

242. Darfeuille-Michaud A, Boudeau J, Bulois P, et al. High prevalence of adherent-invasive *Escherichia coli* associated with ileal mucosa in Crohn's disease. *Gastroenterology*. 2004;127(2):412-421.

243. Nakamoto N, Sasaki N, Aoki R, et al. Gut pathobionts underlie intestinal barrier dysfunction and liver T helper 17 cell immune response in primary sclerosing cholangitis. *Nat Microbiol*. 2019;4(3):492-503.

244. Palmer AC, Sorger PK. Combination cancer therapy can confer benefit via patient-to-patient variability without drug additivity or synergy. *Cell*. 2017;171(7):1678-1691.e13.

245. Vermeire S, Noman M, Van Assche G, Baert F, D'Haens G, Rutgeerts P. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. *Gut*. 2007;56(9):1226-1231.

246. Campieri M, Rizzello F, Venturi A, Poggioli G, Ugolini F. Combination of antibiotic and probiotic treatment is efficacious in prophylaxis of post-operative recurrence of Crohn's disease: a randomized controlled study vs mesalamine. *Gastroenterology*. 2000;118(Suppl):A781.

247. Constante M, Fragoso G, Lupien-Meilleur J, Calvé A, Santos MM. Iron supplements modulate colon microbiota composition and potentiate the protective effects of probiotics in dextran sodium sulfate-induced colitis. *Inflamm Bowel Dis*. 2017;23(5):753-766.

248. Hoppe M, Önning G, Hulthén L. Freeze-dried *Lactobacillus plantarum* 299v increases iron absorption in young females—double isotope sequential single-blind studies in menstruating women. *PLoS One*. 2017;12(12):e0189141. https://doi.org/10.1371/journal.pone.0189141.

249. Fujimori S, Tatsuguchi A, Gudis K, et al. High dose probiotic and prebiotic cotherapy for remission induction of active Crohn's disease. *J Gastroenterol Hepatol*. 2007;22(8):1199-1204.

250. Hu Y, Ye Z, She YQ, et al. Efficacy and safety of probiotics combined with traditional Chinese medicine for ulcerative colitis: a systematic review and meta-analysis. *Front Pharmacol*. 2022;13:844961. https://doi.org/10.3389/fphar.2022.844961.

251. Neurath MF. Cytokines in inflammatory bowel disease. *Nat Rev Immunol*. 2014;14(5):329-342.

252. Steinhart AH, Feagan BG, Wong CJ, et al. Combined budesonide and antibiotic therapy for active Crohn's disease: a randomized controlled trial. *Gastroenterology*. 2002;123(1):33-40.

253. Ganji-Arjenaki M, Rafieian-Kopaei M. Probiotics are a good choice in remission of inflammatory bowel diseases: A meta analysis and systematic review. *J Cell Physiol*. 2018;233(3):2091-2103.

254. Pascal V, Pozuelo M, Borruel N, et al. A microbial signature for Crohn's disease. *Gut*. 2017;66(5):813-822.

255. Costello SP, Hughes PA, Waters O, et al. Effect of fecal microbiota transplantation on 8-week remission in patients with ulcerative colitis: a randomized clinical trial. *JAMA*. 2019;321(2):156-164.

256. Seres Therapeutics. A study to assess efficacy and safety of SER-287 in adults with active mild-to-moderate ulcerative colitis (ECO-RESET). Available from: https://clinicaltrials.gov/ct2/show/study/NCT03759041.

257. Janssen Research & Development, LLC. A study to evaluate the safety and tolerability of JNJ-67670187 in healthy participants. Available from: https://clinicaltrials.gov/ct2/show/NCT03723746.

258. 4D Pharma plc. Study of *Bacteroides thetaiotaomicron* in young people aged 16 to 18 years with stable Crohn's disease. Available from: https://clinicaltrials.gov/ct2/show/NCT02704728.

259. San Giovanni Addolorata Hospital. *Lactobacillus rhamnosus* GG (ATCC 53103) in mild-moderately active UC patients (LGGinUC). Available from: https://clinicaltrials.gov/ct2/show/NCT04102852.

260. VSL Pharmaceuticals. PRObiotic VSL#3® for Maintenance of Clinical and Endoscopic REMission in Ulcerative Colitis (PROREM UC). Available from: https://clinicaltrials.gov/ct2/show/NCT03415711.

261. Massachusetts General Hospital. Effect of a probiotic mixture on the gut microbiome and fatigue in patients with quiescent inflammatory bowel disease. Available from: https://clinicaltrials.gov/ct2/show/NCT03266484.

262. Palumbo VD, Romeo M, Marino Gammazza A, et al. The long-term effects of probiotics in the therapy of ulcerative colitis: a clinical study. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2016;160(3):372-377.

263. Tamaki H, Nakase H, Inoue S, 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. *Dig Endosc*. 2016;28(1):67-74.

264. Bourreille A, Cadiot G, Le Dreau G, et al; FLORABEST Study Group. *Saccharomyces boulardii* does not prevent relapse of Crohn's disease. *Clin Gastroenterol Hepatol*. 2013;11(8): 982-987.

265. Bousvaros A, Guandalini S, Baldassano RN, et al. A randomized, double-blind trial of Lactobacillus GG versus placebo in addition to standard maintenance therapy for children with Crohn's disease. *Inflamm Bowel Dis*. 2005;11(9):833-839.

266. Matthes H, Krummenerl T, Giensch M, Wolff C, Schulze J. Clinical trial: probiotic treatment of acute distal ulcerative colitis with rectally administered *Escherichia coli* Nissle 1917 (EcN). *BMC Complement Altem Med*. 2010;10:13. https://doi.org/10.1186/1472-6882-10-13.

267. Miele E, Pascarella F, Giannetti E, Quaglietta L, Baldassano RN, Staiano A. Effect of a probiotic preparation (VSL#3) on induction and maintenance of remission in children with ulcerative colitis. *Am J Gastroenterol*. 2009;104(2):437-443.

268. Rembacken BJ, Snelling AM, Hawkey PM, Chalmers DM, Axon AT. Non-pathogenic *Escherichia coli* versus mesalazine for the treatment of ulcerative colitis: a randomised trial. *Lancet*. 1999;354(9179): 635-639.

269. Schultz M, Timmer A, Herfarth HH, Sartor RB, Vanderhoof JA, Rath HC. Lactobacillus GG in inducing and maintaining remission of Crohn's disease. *BMC Gastroenterol*. 2004;4:5. https://doi.org/10.1186/1471-230X-4-5.

270. Kruis W, Schütz E, Fric P, Fixa B, Judmaier G, Stolte M. Double-blind comparison of an oral *Escherichia coli* preparation and mesalazine in maintaining remission of ulcerative colitis. *Aliment Pharmacol Ther*. 1997;11(5):853-858.

The emerging microbiome-based approaches to IBD therapy:From SCFAs to urolithin A

Exclude bibliography   On