SUPPLEMENT ARTICLE

New Approaches for Bacteriotherapy: Prebiotics, New-Generation Probiotics, and Synbiotics

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The gut microbiota has a significant role in human health and disease. Dysbiosis of the intestinal ecosystem contributes to the development of certain illnesses that can be reversed by favorable alterations by probiotics. The published literature was reviewed to identify scientific data showing a relationship between imbalance of gut bacteria and development of diseases that can be improved by biologic products. The medical conditions vary from infectious and antibiotic-associated diarrhea to obesity to chronic neurologic disorders. A number of controlled clinical trials have been performed to show important biologic effects in a number of these conditions through administration of prebiotics, probiotics, and synbiotics. Controlled clinical trials have identified a limited number of prebiotics, probiotic strains, and synbiotics that favorably prevent or improve the symptoms of various disorders including inflammatory bowel disease, irritable bowel syndrome, infectious and antibiotic-associated diarrhea, diabetes, nonalcoholic fatty liver disease, necrotizing enterocolitis in very low birth weight infants, and hepatic encephalopathy. Studies have shown that probiotics alter gut flora and lead to elaboration of flora metabolites that influence health through 1 of 3 general mechanisms: direct antimicrobial effects, enhancement of mucosal barrier integrity, and immune modulation. Restoring the balance of intestinal flora by introducing probiotics for disease prevention and treatment could be beneficial to human health. It is also clear that significant differences exist between different probiotic species. Metagenomics and metatranscriptomics together with bioinformatics have allowed us to study the cross-talk between the gut microbiota and the host, furthering insight into the next generation of biologic products.

Keywords. probiotics; prebiotics; synbiotics; lactobacilli; bifidobacteria.

The human gastrointestinal tract is a complex ecosystem that, although sterile at birth, becomes rapidly colonized by microorganisms with a vast microbial population comprising tens of trillions of bacteria and hundreds of different species. The density and diversity increase exponentially moving from the stomach to the colon, where the microbial content is at its highest concentration. The fecal microbiota has been found to be relatively stable over time in individuals, but differs between subjects [1, 2]. The human gut microbiota is mostly dominated by the phyla Firmicutes and Bacteroidetes [2–4] and contains a core microbiome with shared functionality [5]. The microbiota facilitates digestion and aids in providing nutrition and in the shaping of our immune system [6].

Studies in germ-free animals show that commensal microorganisms are necessary for the development and maturation of the intestinal epithelium and immune system [7]. The intestinal microbiota contributes to the defense against pathogens by the mechanism of colonization resistance and fermentation of nondigestible carbohydrates, occurring mostly in the proximal colon. The main products produced by are short chain fatty acids (SCFAs), which include acetate, propionate, and butyrate. Butyrate is a major energy source for intestinal epithelial cells; affects cell proliferation, cell differentiation, mucus secretion, and barrier function; and has anti-inflammatory and antioxidative potential [8]. Hence, the gut microbiota performs a wide variety of metabolic activities that are essential for the host's metabolism.

In this review, we examine the value of probiotics, prebiotics, and synbiotics in alteration of the gut microenvironment leading to favorable effects in a number of

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Table 1. List of Potential Products in Development That Have Biologic Effects Through Improvement in Diversity of Intestinal Flora With Secondary Effects on the Immune System

Product Classification	Compounds in Development	Therapeutic Target	References
Prebiotics	Inulin	Lipid control, cardiovascular effects, cancer prevention	[10–12]
	Xylooligosaccharide	Lipid control, cancer prevention	[13, 14]
	Oligofructose	Cancer prevention, treatment of recurrent CDI	[12, 15, 16]
	Fructooligosaccharide	Lipid control, cardiovascular effects, prevention of atopic dermatitis	[17, 18]
Probiotics	*Saccharomyces boulardii*	Prevention of AAD, prevention and treatment of infectious diarrhea, prevention of CDI, improvement in symptoms of IBS	[19–24]
	Lactobacillus rhamnosus GG	Prevention of AAD, CDI, and infectious diarrhea; treatment of IBS and prevention of atopic dermatitis	[25–31]
	Lactobacillus reuteri (strains SD2112 and RC14)	Treatment of functional bowel disease (eg, IBS) and treatment of vaginosis/vaginitis	[32, 33]
	Lactobacillus plantarum 299V DSM 9843	Treatment of IBS	[34, 35]
	Lactobacillus acidophilus (strain NCDO1748 and other strains)	Prevention of necrotizing enterocolitis, radiation enteritis, and vaginitis	[36–38]
	Lactobacillus casei DN-114001	Prevention of AAD, infectious diarrhea, and CDI	[39, 40]
	Lactobacillus rhamnosus GR-1	Treatment of vaginosis/vaginitis	[33]
	Lactobacillus gasseri SBT2055	Associated with weight loss	[41]
	Escherichia coli DSM 17252	Treatment of IBS	[42]
	Streptococcus faecalis	Treatment of IBS	[43]
	Bifidobacterium infantis B5624	Treatment of IBS	[44]
	Bifidobacterium bifidum strain NCDO1463	Treatment of necrotizing enterocolitis	[45]
	Bifidobacterium lactis	Prevention of atopic dermatitis	[46]
	Lactobacillus brevis CD2	Reduce incidence of radiation- and chemotherapy-induced mucositis	[47]
	Lactobacillus casei, *Lactobacillus acidophilus* (Bio-K+ CL1285)	Prevention of AAD and CDI	[48]
	Eight probiotic strains (VSL#3)[a]	Management of IBS, IBD, and pouchitis; prevention of radiation-induced diarrhea	[49–55]
Synbiotics	*Lactobacillus acidophilus*, *Bifidobacterium bifidum*, and fructooligosaccharides	Increase HDL cholesterol and reduce fasting glycemia	[56]
	Bifidobacterium and fructooligosaccharides	Treatment of hepatic encephalopathy	[57]

Abbreviations: AAD, antibiotic-associated diarrhea; CDI, *Clostridium difficile* infection; HDL, high-density lipoprotein; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.

[a] *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus bulgaricus*, *Streptococcus thermophilus*.

disorders, topics of growing scientific interest [9]. We will begin with definitions, present the various agents that have been evaluated in clinical settings, discuss mechanism of action of these flora-enhancing agents and their clinical value as seen in scientific and controlled trials, and end with a perspective on future studies and applications.

DEFINITIONS

Bacteriotherapy includes 3 slightly different agents: probiotics, prebiotics, and synbiotics. Probiotics are defined in this review as living bacteria or fungi that confer a health benefit for the host. Prebiotics are nondigestible compounds that lead to favorable changes in the intestinal microbiota, and synbiotics are defined as products that contain both probiotics and prebiotics.

CLASSIFICATION OF FLORA-ALTERING BIOLOGIC AGENTS

Table 1 lists the studied agents that have been evaluated in patients with one of several medical conditions, including inflammatory bowel disease, irritable bowel syndrome, Crohn disease, hepatic encephalopathy, obesity, atopic dermatitis, diabetes, cancer, necrotizing enterocolitis, and hepatic encephalopathy.

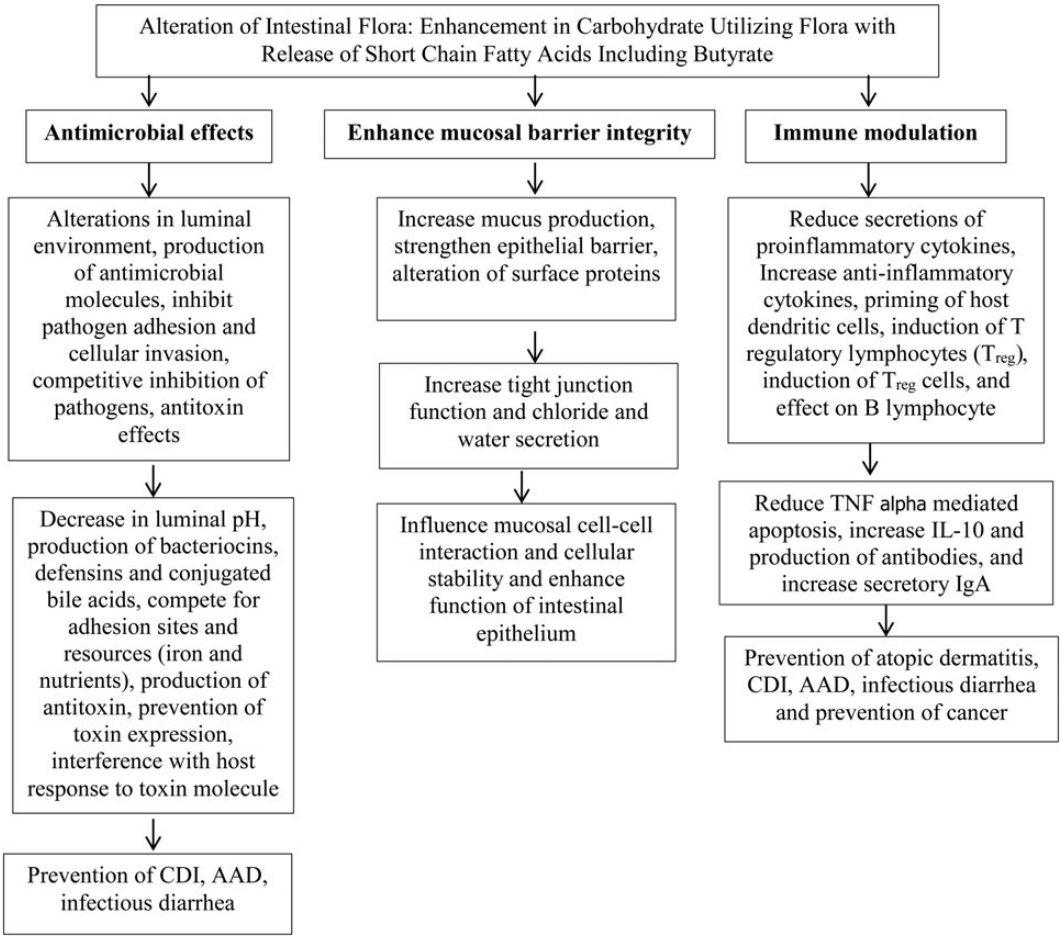

Figure 1. Biologic effects and mechanisms of action of prebiotics, probiotics, and synbiotics. Abbreviations: AAD, antibiotic-associated diarrhea; CDI, *Clostridium difficile* infection; IgA, immunoglobulin A; IL-10, interleukin 10; TNF, tumor necrosis factor.

MECHANISMS OF ACTION OF PROBIOTICS

There are 3 general mechanisms by which probiotics appear to exert their beneficial effects, with important differences seen between probiotic species and strains: antimicrobial effects, enhancement of mucosal barrier integrity, and immune modulation (Figure 1). Probiotics exert antimicrobial effects by release in the intestinal environment of antimicrobial molecules and by taking up space, limiting growth of other microbes. The important benefits of probiotics come from their ability to metabolize complex carbohydrates and produce lactic acid and SCFAs such as butyrate [58, 59]. Butyrate reduces bacterial translocation, improves the organization of tight junctions [60], and stimulates the synthesis of mucin, a glycoprotein maintaining the integrity of the intestinal epithelium [61]. Understanding probiotic action along with increasing knowledge of probiotics on the host immune system is likely to offer useful and promising means to modulate host immunity for prevention and treatment of a broad range of human disorders. We will consider the 3 general functions of probiotics.

ANTIMICROBIAL EFFECTS OF MICROBIAL FLORA

Probiotic strains alter the luminal environment, decrease adhesion and cellular invasion, and can produce antibacterial products (eg, bacteriocins, hydrogen peroxide, and organic acids) that can inhibit the growth of pathogens. Several lactobacilli are responsible for producing bacteriocins [62]. The inhibitory action of these bacteriocins varies from inhibiting other lactobacilli to directly inhibiting a wider range of gram-positive, gram-negative bacteria, viruses, and certain fungi [63]. Another probiotic, *Lactobacillus salivarius* subspecies *salivarius* UCC118, produces a 2-peptide bacteriocin, ABP-118, which inhibits several pathogens including *Enterococcus*, *Bacillus*, *Listeria*, *Staphylococcus*, and *Salmonella* species [64].

Hydrolytic enzymes produced by some probiotics contribute to the increase of lactic acid, propionic acid, butyric acid, and other SCFAs in the intestinal lumen, reducing the luminal pH. Maintaining a lower pH creates a physiologically restrictive environment that can inhibit the growth and colonization by pathogenic bacteria. This was demonstrated in a study of mice infected with Shiga toxin–producing *Escherichia coli* O157:H7. Mice given the probiotic *Bifidobacterium breve* were found to have lower luminal pH via the production of a high concentration of acetic acid, consequently increasing animal survival [65]. This finding was confirmed in humans with ulcerative colitis given the probiotic preparation VSL#3, where a significant decrease in pH was seen [66].

ENHANCE MUCOSAL BARRIER INTEGRITY

Probiotics compete with pathogens and prevent their invasion through the epithelium by their ability to adhere to the intestinal epithelium and mucus. This mechanism inhibits the mucosal and epithelial adherence of pathogens in the intestinal system [67].

Probiotics also compete with other microorganisms for limiting resources. Iron is one such limited resource, as it is a necessary element for nearly all microorganisms. For example, the probiotic *E. coli* Nissle 1917 possesses multiple iron uptake mechanisms, enabling it to effectively take up this limited environmental iron, while simultaneously competitively inhibiting of the growth of other intestinal microbes and pathogens [68].

Intestinal barrier function is maintained by mucus production, chloride and water secretion, and tight junctions, which bind the apical portions of epithelial cells. Disruption of the epithelial barrier is seen in several conditions including infectious diarrhea [69], inflammatory bowel disease [70, 71], and autoimmune diseases including type 1 diabetes mellitus [72]. Enhancement of the mucosal barrier may be a crucial mechanism by which probiotic bacteria benefit the host in these diseases. In a study examining mice deficient in interleukin 10 (IL-10), the addition of *Lactobacillus* species was shown to improve barrier integrity in this fashion, preventing the development of colitis [73].

IMMUNE MODULATION

Probiotics can alter mucosal immunity considerably as they are able to affect many host cell types involved in the local and systemic immune responses, including epithelial cells, dendritic cells (DCs), T cells, regulatory T (T_{reg}) cells, monocytes/macrophages, immunoglobulin A (IgA)–producing B cells, natural killer cells, and by induction of T-cell apoptosis [74].

Probiotic bacteria influence intestinal epithelial cells through pattern recognition molecules or Toll-like receptors (TLRs), such as TLR2 and TLR4. These interactions may stimulate the production of various protective cytokines, such as IL-10 and transforming growth factor β, that can inhibit epithelial cell apoptosis and enhance epithelial cell regeneration [75]. This effect is supported by a study in which the probiotic *Lactobacillus rhamnosus* GG prevented cytokine-induced apoptosis in intestinal epithelial cells [76].

Probiotic bacteria also have an effect on intestinal DCs, which extend processes through the epithelium into the gut lumen and are able to present antigens that are important in early bacterial recognition and in shaping T-cell responses. DCs have the ability to recognize and respond to different bacteria by linking the innate immune system to the adaptive immune response and to develop T- and B-cell responses [77–79]. In addition, T_{reg} cells are also induced by some probiotics, and this may explain how probiotics can exert an anti-inflammatory effect and are beneficial in the treatment of a number of inflammatory diseases, including atopic dermatitis and Crohn disease [80]. Furthermore, probiotic bacteria may also modulate the immune response to protect against potentially harmful antigens via B lymphocytes and antibody production. Children with acute rotavirus diarrhea given *L. rhamnosus* GG were better able to potentiate a nonspecific humoral immune response, shown by increases in immunoglobulin G, IgA, and immunoglobulin M secretion from circulating lymphocytes, resulting in significantly shorter duration of diarrhea [81].

PREBIOTICS

Prebiotics are nondigestible oligosaccharides, such as fructooligosaccharides, galactooligosaccharides, lactulose, and inulin, which have the potential to stimulate growth of selective and beneficial gut bacteria, particularly lactobacilli and bifidobacteria [17, 82]. Because of their composition, prebiotics cannot be adsorbed until they reach the colon, where they can be fermented by a specific microbe into SCFAs and lactate [17]. Recent evidence shows that prebiotics are able to increase the production of SCFAs, which in turn modulates cytokine production within the gut mucosa by altering the gut flora composition. In human studies, administration of 10 g of transgalactooligosaccharides was shown to increase the number of bifidobacteria and modify the colonic fermentation metabolism of the gut flora [83].

Prebiotics can also be used as energy substrates by intestinal bacteria. When inulin-type fructan prebiotics were given to mice, the number of bifidobacteria increased significantly, with an inverse correlation with the levels of lipopolysaccharide, development of glucose tolerance, and fat mass [84, 85]. Additionally, in clinical trials using these inulin-type fructans [86], prebiotics have shown positive weight loss results in overweight and obese populations.

Prebiotics have also shown to be useful in hypercholesterolemia. A randomized, double-blind, crossover study in hamsters

Table 2. Clinical Evidence of Efficacy of Probiotics in Which Controlled Trials Have Been Conducted

Target Condition	Probiotic Agent	Study Outcome	References
Treatment of infectious diarrhea in children	*Lactobacillus rhamnosus* strains	Randomized, double-blind, placebo-controlled trial. *L. rhamnosus* strains (573L/1, 573L/2, 573L/3) dose of 1.2×10^{10} CFU vs placebo, twice daily for 5 d. Mean duration of diarrhea in the treated group: 84 ± 56 h vs placebo: 96 ± 72 h ($P = .36$). In rotavirus infection: 76 ± 35 h vs 115 ± 67 h ($P = .03$), respectively.	[27, 94]
Prevention of infectious diarrhea	*Bifidobacterium lactis* and *Lactobacillus reuteri*	Randomized, double-blind, placebo-controlled trial. Infants in the control group were found to have a mean of 0.31 episodes of diarrhea (95% CI, .22–.44 episodes) vs 0.12 episodes (95% CI, .05–.21 episodes) and 0.02 episodes (95% CI, .01–.05 episodes) in the *B. lactis and L. reuteri*–supplemented study groups, respectively ($P = .001$).	[95]
Prevention of AAD	*Lactobacillus casei*, *Lactobacillus acidophilus* (Bio-K+ CL1285)	Randomized, double-blind, placebo-controlled dose-ranging study. Patients were randomized to 1 of 3 groups: high-dose (2 probiotics capsules/day) and low-dose probiotic (1 probiotic capsule, 1 placebo capsule/day) and placebo group (2 placebo capsules/day). High dose (15.5%) had a lower AAD incidence vs low dose (28.2%). Each probiotic group had a lower AAD incidence vs placebo (44.1%). In patients who acquired AAD, high dose (2.8 d) and low dose (4.1 d) had shorter symptom duration vs placebo (6.4 d).	[48]
	Lactobacillus casei, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus*	Randomized, double-blind, placebo-controlled trial using 100 g (97 mL) probiotic mixture twice/day. The placebo group received a long-life sterile milkshake. Seven of 57 (12%) of the probiotic group developed diarrhea associated with antibiotic use vs 19/56 (34%) in the placebo group ($P = .007$).	[39]
	Lactobacillus acidophilus, *Lactobacillus casei* (Bio-K+ CL1285)	Randomized, double-blind, placebo-controlled trial, using 49 g (50×10^9 CFU of *L. acidophilus* CL1285 and *L. casei* (Bio-K+ CL1285) once daily for 2 d, followed by 98 g of Bio-K+ CL1285 once daily over duration of antibiotic treatment. AAD occurred in 7/44 patients (15.9%) in the *Lactobacilli* group and in 16/45 patients (35.6%) in the placebo group (OR, 0.34; 95% CI, .125–.944; $P = .05$).	[96]
	Saccharomyces boulardii	Double-blind, placebo-controlled, parallel group study. Lyophilized *S. boulardii* or placebo (1 g/day). Significantly fewer patients receiving *S. boulardii* (7/97 [7.2%]) developed AAD vs 14/96 (14.6%) on placebo ($P = .02$). The efficacy of *S. boulardii* for the prevention of AAD was 51%.	[19]
Prevention of CDAD	*Lactobacillus casei*, *Lactobacillus acidophilus* (Bio-K+ CL1285)	Randomized, double-blind, placebo-controlled dose-ranging study. Patients were randomized to 1 of 3 groups: high-dose (2 probiotics capsules/day) and low-dose probiotic (1 probiotic capsule, 1 placebo capsule/day) and placebo group (2 placebo capsules/day). High-dose probiotic (1.2%) had a lower CDI incidence vs low-dose probiotic (9.4%). Each treatment group had a lower CDI incidence vs placebo (23.8%).	[48]
	Lactobacillus casei, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus*	Randomized, double-blind, placebo-controlled trial of 100 g (97 mL) probiotic mixture twice/day. No one in the probiotic group and 9/53 (17%) in the placebo group had diarrhea caused by CDI ($P = .001$). The absolute risk reduction was 17% (95% CI, 7%–27%), and the NNT was 6 (NNT, 4–14).	[39]
	Saccharomyces boulardii	A meta-analysis of the 4 studies that used *S. boulardii* showed a trend toward lower CDI rates in the probiotic group, but this result was not significant (risk ratio, 0.70; 95% CI, .29–1.69) and there was more heterogeneity ($I^2 = 17.2\%$; $P = .30$).	[21]

Table 2 continued.

Target Condition	Probiotic Agent	Study Outcome	References
Prevention of recurrent CDAD	*Saccharomyces boulardii*	500 mg *S. boulardii* given twice daily for 4 wk during and after antibiotic treatment for CDI yielded an overall CDI recurrence rate of 26.3% comparing to a 44.8% CDI recurrence rate in the placebo group ($P = .05$).	[22]
	Saccharomyces boulardii	A significant decrease in recurrences was observed only in patients treated with high-dose vancomycin (2 g/day) and *S. boulardii* (1 g/day for 28 d) (16.7%), compared with those who received high-dose vancomycin and placebo (50%; $P = .05$).	[23]
	Lactobacillus rhamnosus GG	Five patients with multiple recurrences of CDI were treated successfully with LGG in an open-label study. In another open-label, uncontrolled study, 4 children with multiple recurrences of CDI had resolution of their infection after 2 wk of LGG administration.	[26, 97, 98]
IBS	VSL#3	Randomized, double-blind, parallel group study. Treatment with VSL#3 was associated with reduced flatulence over the entire treatment period (placebo: 39.5 ± 2.6 vs VSL#3: 29.7 ± 2.6; $P = .011$). Colonic transit was retarded with VSL#3 vs placebo (colon geometric center, 2.27 ± 0.20 vs 2.83 ± 0.19; $P = .05$).	[51]
	Bifidobacterium bifidum MIMBb75	Randomized, double-blind, placebo-controlled trial. *B. bifidum* MIMBb75(1×10^9 CFU) resulted in a greater reduction in global IBS symptoms, with more patients consuming the probiotic (47%) than the placebo (11%) reporting adequate relief of their symptoms.	[99]
	Lactobacillus plantarum (DSM 9843)	Randomized, double-blind, placebo-controlled trial. Study group received 400 mL per day of a rose-hip drink of 5×10^7 CFU/mL *L. plantarum* (DSM 9843) and 0.009 g/mL oat flour; placebo group received a plain rose-hip drink. Flatulence was rapidly and significantly reduced in the test group compared with the placebo group. Abdominal pain was reduced in both groups. At the 12-month follow-up, patients in the test group maintained better overall GI function than control patients.	[100]
	Lactobacillus plantarum 299V (LP299V)	Randomized, double-blind, placebo-controlled trial. All 10 patients in the LP299V group (5×10^7 CFU/mL) reported resolution of their abdominal pain compared with 11 patients from a placebo group ($P = .0012$). An improvement in IBS symptoms was noted in 95% of patients in the LP299V group vs 15% of patients in the placebo group ($P < .0001$).	[35]
	Lactobacillus plantarum 299v (DSM 9843)	Randomized, double-blind, placebo-controlled, parallel designed study, using 1 capsule (10×10^9 CFU per capsule) of *L. plantarum* 299v (DSM 9843) or placebo. After 4 wk, both pain severity (0.68 + 0.53 vs 0.92 + 0.57; $P < .05$) and daily frequency (1.01 + 0.77 vs 1.71 + 0.93; $P < .05$) were lower with *L. plantarum* 299v (DSM 9843) than with placebo. Similar results were obtained for bloating. At week 4, 78.1% of the patients scored the symptomatic effect of *L. plantarum* 299v (DSM 9843) as excellent or good vs only 8.1% for placebo ($P < .01$).	[34]
	Bifidobacterium infantis 35624	*B. infantis* 35624 experienced a greater reduction in symptom scores. Another study showed that *B. infantis* 35624 at a dose of 1×10^8 CFU was significantly superior to placebo. The improvement in global symptom assessment exceeded placebo by >20% ($P < .02$).	[44, 101]
	Escherichia coli (DSM 17252)	Randomized, double-blind, placebo-controlled trial. The general symptom score to the drug was 27/148 (18.2%) vs placebo with 7/150 (4.67%) ($P = .000397$). The improvement in abdominal pain score was 28/148 (18.9%) vs 10/150 (6.67%) for placebo ($P = .001649$).	[42]
	Streptococcus faecium	Double-blind, placebo-controlled trial. After 4 wk, 81% of the Paraghurt-treated (freeze-dried culture of *S. faecium)* and 41% of the placebo-treated patients had improved according to physicians' overall assessment ($P = .002$).	[43]

Table 2 continued.

Target Condition	Probiotic Agent	Study Outcome	References
Remission of ulcerative colitis	VSL#3	Randomized, double-blind, placebo-controlled trial using 3.6×10^{12} CFU of VSL#3 vs placebo. There were no significant differences in obtaining clinical remission, but there was a significant clinical response in the VSL#3 group.	[50]
	VSL#3	Randomized, double-blind, placebo-controlled trial finding the VSL#3 (3.6×10^{12} CFU) group to have significantly higher remission rates (42.9% vs 15.9%) and endoscopic healing (32% vs 14.7%).	[49]
	E. coli Nissle 1917	Randomized, double-blind, placebo-controlled trial. Doses of 40 mL, 20 mL, or 10 mL enemas containing ECN (1×10^8 CFU/mL) or placebo, concluding that remission rates significantly decreased according to dosing; 53%, 44%, and 27%, respectively.	[102]
Maintenance of ulcerative colitis	*E. coli* Nissle 1917	ECN at 200 mg/d was similar in efficacy to 1500 mg of mesalamine for maintaining UC in remission. In children with UC, VSL#3 also showed improved rates of maintenance of remission. Three of 14 (21.4%) patients treated with VSL#3 and IBD therapy and 11 of 15 (73.3%) patients treated with placebo and IBD therapy relapsed within 1 y of follow-up ($P = .014$; RR, 0.32; CI = .025–.773; NNT, 2).	[103, 104]
Crohn's disease		Studies have found *Lactobacillus* GG and other lactobacilli not to be superior to placebo for inducing or maintaining remission in CD or for the prevention of postoperative CD. In addition, there are also no solid data to support the use of ECN or *S. boulardii* in Crohn's disease.	[105–110]
Prevention and remission of pouchitis	VSL#3	Patients given 2 sachets twice daily (3.6×10^{12} CFU/day) for 4 wk; 16/23 patients (69%) were in remission after treatment. The median total Pouchitis Disease Activity Index scores before and after therapy were 10 (range, 9–12) and 4 (range, 2–11), respectively ($P < .01$). All 16 patients who went into remission maintained remission during maintenance treatment.	[52]
Maintenance of pouchitis	VSL#3	Three randomized, placebo-controlled studies were performed. ITT analyses revealed significantly lower relapse rates after 9 or 12 mo intervention in UC patients with a pouch, either after inducing remission by antibiotics (n = 40 and n = 36) or starting 1 wk after ileostomy closure (n = 40). The 3 randomized placebo-controlled studies were included in the meta-analysis, revealing a pooled RR of 0.17 (95% CI, .09–.33).	[53, 54, 111]
Prevention of atopic dermatitis	*Lactobacillus rhamnosus*	Meta-analysis of double-blinded, randomized controlled trials of 25 clinical trials. Probiotics were effective in reducing total IgE (mean reduction: −7.59 U/mL; 95% CI, −14.96 to −.22; $P = .044$). Probiotics significantly reduced the risk of atopic sensitization when administered prenatally (RR: 0.88; 95% CI, .78–.99; $P = .035$) and postnatally (RR: 0.86; 95% CI, .75–.98; $P = .027$).	[28]
Treatment of atopic dermatitis	Probiotic mixture (*Bifidobacterium bifidum*, *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Lactobacillus salivarius* strains)	Randomized, double-blind, placebo-controlled trial. Patients received 2 bags of 2×10^9 probiotic mixture. Probiotic group effectively reduced the SCORAD index and serum cytokines interleukin 5, interleukin 6, interferon γ, and total serum IgE levels vs the placebo group.	[112]
Prevention of radiation-induced diarrhea	VSL#3	Randomized, double-blind, placebo-controlled trial. High-potency VSL#3 (1 sachet 3 times daily, each sachet of VSL#3 contained 4.5×10^{11}/g) vs placebo starting from day 1 of radiation therapy. More placebo patients had radiation-induced diarrhea than VSL#3 patients (124/239 patients [51.8%] and 77/243 patients [31.6%]; $P < .001$), and more patients given placebo suffered grade 3 or 4 diarrhea vs VSL#3 recipients (55.4% and 1.4%; $P < .001$). Daily bowel movements were 14.7 ± 6 and 5.1 ± 3 among placebo and VSL#3 recipients, respectively ($P < .05$), and the mean time to the use of loperamide was 86 ± 6 h for placebo patients and 122 ± 8 h for VSL#3 patients ($P < .001$).	[55]

Table 2 continued.

Target Condition	Probiotic Agent	Study Outcome	References
Reduce incidence of radiation- and chemotherapy-induced mucositis	*Lactobacillus brevis* CD2	Randomized, double-blind, placebo-controlled trial. Six lozenges per day of 2×10^9 viable cells of *L. brevis* CD2 as the active ingredient were given. Grade III and IV mucositis developed in 52% of patients in the *L. brevis* CD2 group and 77% in the placebo group ($P < .001$). Anticancer treatment completion rates were 92% in the *L. brevis* CD2 group and 70% in the placebo group ($P = .001$). A larger proportion of patients remained free of mucositis when treated with *L. brevis* CD2 (28%) vs placebo (7%).	[47]
Prevention of necrotizing enterocolitis	*Lactobacillus* alone or in combination with *Bifidobacterium*	Meta-analysis. Enteral probiotic supplementation significantly reduced the incidence of severe NEC (stage II or more) (typical RR, 0.43; 95% CI, .33–.56; 20 studies, 5529 infants) and mortality (typical RR, 0.65; 95% CI, .52–.81; 17 studies, 5112 infants). The included trials reported no systemic infection with the supplemental probiotic organism(s).	[113]
Treatment of hepatic encephalopathy	*Bifidobacterium* combined with fructooligosaccharide	*Bifidobacterium* + FOS–treated patients compared with lactulose-treated patients showed a significant decrease of ammonia fasting HE1 ($P < .001$), and a significant increase of symbol digit modalities test ($P < .001$) and block design test ($P < .001$).	[57]

Abbreviations: AAD, antibiotic-associated diarrhea; CD, Chrohn's disease; CDAD, *Clostridium difficile*–associated diarrhea; CDI, *Clostridium difficile* infection; CFU, colony-forming unit; CI, confidence interval; DSM, design structure matrix; ECN, *Escherichia coli* Nissle 1917; FOS, fructooligosaccharide; GI, gastrointestinal; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IgE, immunoglobulin E; ITT, intent-to-treat; LGG, *Lactobacillus rhamnosus* GG; NEC, necrotizing enterocolitis; NNT, number needed to treat; OR, odds ratio; RR, relative risk; SCORAD, scoring atopic dermatitis; UC, ulcerative colitis.

using inulin as a prebiotic resulted in a 29% decrease in total cholesterol and a 63% decrease in triglycerides compared to controls over a 5-week study [10]. In another study, 40 male Sprague-Dawley rats given xylooligosaccharide as a prebiotic showed a 27% reduction in triglycerides [14]. In a randomized crossover human study, inulin administration to 12 men with hypercholesterolemia led to a mean reduction in serum triglycerides by 40 mg/dL ($P = .05$) [11].

Prebiotics have also shown to reduce cancer incidence in animal models. Rats and mice fed with inulin and/or oligofructose had decreased numbers of chemically induced precancerous lesions [87, 88]. In another study testing inulin and oligofructose, breast cancer incidence in rats and mice [89] and large intestinal tumor incidence [90] was lowered by adding 5%–15% inulin or oligofructose to the diet. The result was even more striking when a combination of prebiotics and probiotics was given [91].

The recurrence of *Clostridium difficile*–associated diarrhea can also be decreased with prebiotics. In a randomized study of 142 patients with *C. difficile*–associated diarrhea receiving oligofructose or placebo for 30 days in addition to specific antibiotic treatment, the recurrence rate was lowered from 34.3% in controls to 8.3% in the oligofructose recipients ($P < .001$) [15].

Clinical data from the use of prebiotics in allergic conditions have been encouraging. A recent meta-analysis showed that using prebiotics resulted in a 32% reduction in the incidence of pediatric atopic dermatitis [92]. Another meta-analysis by Osborn and Sinn [93] exploring the effect of specific prebiotics in the prevention of allergy found that using a combination of galactooligosaccharide and fructooligosaccharide was associated with a significant reduction in eczema (relative risk, 0.68). The reduction of atopic eczema by prebiotics was also supported in another study of 200 infants who were administered fructooligosaccharide/galactooligosaccharide-enriched formula or placebo. At 6 months of age, the incidence of atopic eczema was reduced from 23.1% (95% confidence interval [CI], 16.0%–32.1%) in the placebo group to 9.8% (95% CI, 5.4%–17.1%) in the prebiotic-supplemented group [18].

PROBIOTICS

Probiotics have been included in a number of controlled clinical trials in patients with infectious diarrhea and for prevention of antibiotic-associated diarrhea, therapy and prevention of *C. difficile* infection, inflammatory bowel disease, irritable bowel syndrome, prevention of radiation- or chemotherapy-induced sequelae, necrotizing enterocolitis, hepatic encephalopathy, and atopic dermatitis (Table 2).

Clinical trials have tested both single strains and mixtures of probiotics, with results depending upon the strain and the probiotic dose. The most common species that are used as single species and that have been studied are *L. rhamnosus* GG, *Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus johnsonii*, *Bifidobacterium lactis*, and *Saccharomyces boulardii* [114].

Table 3. Clinical Evidence of Efficacy of Synbiotics in Which Controlled Trials Have Been Conducted

Target Condition	Synbiotic Agent	Study Outcome	Reference
Treatment of infectious diarrhea in children	*Bifidobacterium lactis* B94 plus inulin	Randomized, double-blind, placebo-controlled trial. N = 156. *B. lactis* B94 dose of 5×10^{10} CFU plus 900 mg inulin (Maflor sachet) was given once a day for 5 days. The duration of diarrhea was significantly reduced in the synbiotic group vs the placebo group (3.9 ± 1.2 d vs 5.2 ± 1.3 d, respectively; $P < .001$). The decrease was most pronounced in synbiotic-group cases of rotavirus diarrhea, (3.2 ± 1.3 d vs 5.2 ± 1.3 d, respectively; $P = .001$).	[115]
Constipation in adult women	*Lactobacillus* and *Bifidobacterium* strains plus FOS	Randomized, double-blind, placebo-controlled trial. N = 100. Each LACTOFOS sachet contained 6 g of FOS and 10^8–10^9 bacteria of *Lactobacillus paracasei* (Lpc-37), *Lactobacillus rhamnosus* (HN001), *Lactobacillus acidophilus* (NCFM), and *Bifidobacterium lactis* (HN019). Patients were given 2 daily doses of each for 30 days. Synbiotic group had increased frequency of evacuation, as well as stool consistency and shape nearer normal parameters than the placebo group, with significant benefits starting during the second and third weeks, respectively (interaction group/time, $P < .0001$).	[116]
Treatment of irritable bowel syndrome	*Bacillus coagulans* and FOS	Randomized, double-blind, placebo-controlled trial. N = 85. *B. coagulans* (15×10^7 CFU) and 100 g FOS (Lactol). Patients received synbiotic 3 × /d for 12 weeks. After treatment, more reduction in abdominal pain frequency was observed with synbiotic vs placebo (score reduction 4.2 ± 1.8 vs 1.9 ± 1.5; $P < .001$). Diarrhea frequency was decreased in the synbiotic group, but not in the placebo group (score reduction 1.9 ± 1.2 vs 0.0 ± 0.5; $P < .001$).	[117]
Crohn disease	*Bifidobacterium longum* and inulin/oligofructose (Synergy 1)	Randomized, double-blind, placebo-controlled trial. N = 35. *B. longum*, 2×10^{11} CFU plus 6 g of Synergy 1 were taken 2× daily for 6 months. Significant improvements in clinical outcomes occurred with synbiotic consumption, with reductions in both Crohn disease activity indices ($P = .020$) and histological scores ($P = .018$). Significant reductions occurred in TNF-α expression in synbiotic patients at 3 months ($P = .041$). Mucosal bifidobacteria proliferated in synbiotic patients.	[118]
Treatment of ulcerative colitis	*Bifidobacterium longum* plus psyllium	Randomized controlled trial. N = 120. *B. longum* 2×10^9 CFU and 8 g doses of psyllium. The primary endpoint was scores on the IBD Questionnaire, which assesses health-related quality of life in IBD at 4 weeks. Results showed a statistically significant improvement in scores (168 to 176; $P = .03$) for the synbiotic group at the end of the study. Individual scores for synbiotics group—systemic and social functions ($P = .008$ and $P = .02$).	[119]
Treatment of ulcerative colitis	*Bifidobacterium breve* strain Yakult and GOS	Randomized controlled study. *B. breve* strain Yakult (10^9 CFU/g) 3× a day, and 5.5 g of GOS per day for 1 year. There was significantly improvement of endoscopic grading (Matts classification) in the synbiotic group vs the standard therapy group ($P < .05$).	[120]
Necrotizing enterocolitis in very low birth weight infants	*Bifidobacterium lactis* plus inulin	Randomized, double-blind, placebo-controlled trial. N = 400. 30 mg of *B. lactis* (5×10^9 CFU) plus 900 mg of inulin. One sachet per day with breast milk or formula for 8 weeks before discharge or death. The rate of NEC was lower in probiotic (2.0%) and synbiotic (4.0%) groups vs prebiotic (12.0%) and placebo (18.0%) groups ($P < .001$).	[121]
Weight gain in children with failure to thrive	*Bacillus coagulans* plus FOS	Randomized, triple-blinded, placebo-controlled. N = 84. *B. coagulans* (1.5×10^8 CFU) and 100 mg FOS. Synbiotic mixture were administered for 6 months. The increase in weight was significantly higher in synbiotics group than in controls ($P < .05$). At the beginning, the mean weights were 10.25 ± 0.20 kg and 10.750 ± 0.160 kg in intervention and control groups, respectively. After 6 months, the mean weights became 12.280 ± 0.190 and 11.760 ± 0.17 kg in intervention and control groups, respectively.	[122]
Diabetes	*Lactobacillus sporogenes* plus inulin	Randomized double-blind, crossover controlled trial. N = 62. *L. sporogenes* (1×10^7 CFU) plus 0.04 g inulin, packed in 9-g packages taken 3× a day for 6 weeks. There was a significant decrease in serum insulin levels (changes from baseline: –1.75 ± 0.60 vs 0.95 ± 1.09 mIU /mL; $P = .03$), a significant decrease in hs-CRP levels (–1057.86 ± 283.74 vs 95.40 ± 385.38 ng/mL; $P = 0.01$), a significant increase in plasma total GSH (319.98 vs 19.73 mmol/L; $P < 0.001$) and serum uric acid levels (0.7 vs 0.1 mg/dL; $P = .04$).	[123]
Nonalcoholic fatty liver disease	*Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Bifidobacterium longum*, *and Lactobacillus bulgaricus* and FOS (Protexin)	Randomized, double-blind, placebo-controlled trial. N = 52. Each Protexin capsule contained 2×10^8 CFU of probiotic mixture and FOS. The synbiotic mixture was supplemented 2× daily for 28 wk. There was a significant reduction of ALT in the synbiotic group. ALT, –25.1 (–26.2, –24) vs –7.29 (–9.5, –5.1) IU/L, $P < .001$; AST, –31.33 (–32.1, –30.5) vs –7.94 (–11.1, –4.8) IU/L, $P < .001$; gamma-glutamyltransferase, –15.08 (–15.5, 214.7) vs –5.21 (–6.6, –3.9) IU/L, $P < .001$; hs-CRP, –2.3 (–3, –1.5) vs –1.04 (–1.5, –0.6) mmol/L, $P < .05$; TNF-α, –1.4 (–1.7, –1.1) vs –0.59 (–0.8, –0.3) mmol/L, $P < .001$; total nuclear factor kB p65, –0.016 (–0.022, –0.011) vs 0.001 (–0.004, –0.007) mmol/L, $P < .001$; and fibrosis score as determined by transient elastography, –2.98 (–3.6, –2.37) vs –0.77 (–1.32, –0.22) kPa, $P < .001$.	[124]

Table 3 continued.

Target Condition	Synbiotic Agent	Study Outcome	Reference
Lipid profile and glucose homeostasis in overweight or obese adults	*Lactobacillus* combined with inulin or *Lactobacillus* and *Bifidobacterium* combined with FOS	Meta-analysis study. Four synbiotic randomized controlled trials. A significant reduction in the triglycerides (SMD −0.43; 95% CI, −.70 to .15; $P < .05$) and fasting insulin (SMD −0.39; 95% CI −.75 to −.02; $P = .04$) after synbiotic supplementation.	[125]
Surgery for chronic pancreatitis	*Streptococcus faecalis*, *Clostridium butyricum*, *Bacillus mesentericus*, *Lactobacillus sporogenes* plus FOS	Randomized, single-blind, placebo-controlled trial. N = 75. *S. faecalis* T-110 (6×10^7), *C. butyricum* TOA (4×10^7 CFU), *B. mesentericus* TO-A (2×10^7 CFU), *L. sporogenes* (1×10^8 CFU) plus FOS. The synbiotic was given for 5 days prior and 10 days after the surgery. Primary study endpoint was the occurrence of postoperative infection during the first 30 days. The incidence of postoperative infectious complications (12.8% vs 39%; $P < .05$), duration of antibiotic therapy ($P < .05$), and length of hospital stay ($P < .05$) were significantly lower in the synbiotic group.	[126]
Radiation-induced acute proctitis	*Lactobacillus reuteri* plus inulin	Randomized, double-blind, placebo-controlled trial. N = 20. One sachet contained 5 g *L. reuteri* (10^8 CFU) and 4.3 g of inulin (Nestle). 1 sachet was given 1× a day for 1 wk before the beginning of radiation therapy, increasing the dose to 2 sachets/d for next 4 wk. The complete questionnaire score was higher in the second (23 [21–30] vs 26.5 [22–34], $P < .05$) and third (23 [21–32] vs 27.5 [24–33], $P < .01$) weeks in the placebo group. Proctitis symptoms were highest scored in the placebo group in both the second (19.5 [16–25]) and third (19 [17–24]) weeks than in the synbiotic group (week 2: 16.5 [15–20], $P < .05$; week 3: 17 [15–23], $P < .01$).	[127]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CFU, colony-forming units; CI, confidence interval; FOS, fructooligosaccharides; GOS, galactooligosaccharide; GSH, glutathione; hs-CRP, high-sensitivity C-reactive protein; IBD, inflammatory bowel disease; LACTOFOS, symbiotic mixture includes *Lactobacillus*, *Bifidobacterium* strains and fructo-oligosaccharides; NEC, necrotizing enterocolitis; SMD, standardized mean difference; TNF, tumor necrosis factor; TOA, specific probiotic strain designation.

SYNBIOTICS

The concept of a synbiotic is to combine a probiotic and a prebiotic to facilitate the survival and activity of proven probiotics in vivo, as well as stimulating indigenous anaerobic bacteria. Probiotics and prebiotics work synergistically to provide a combined benefit. Some of the studies that have shown positive synergistic effects of synbiotics on obesity, diabetes, nonalcoholic fatty liver disease, necrotizing enterocolitis in very low birth weight infants, and treatment of hepatic encephalopathy are listed in Table 3.

FUTURE STUDIES AND APPLICATION

Most of the currently commercialized probiotics used to treat and prevent medical conditions are limited to the *Lactobacillus* and *Bifidobacterium* strains previously discussed. The efficacy of the existing probiotics used for the treatment or prevention of medical conditions is limited. Information gained from previous studies are helping to set a rationale for selection of a next generation of probiotics such as *Faecalibacterium prausnitzii* [128], Clostridia clusters IV, XIVa, and XVIII [129], *Akkermansia muciniphila* [130], and *Bacteroides uniformis* [131]—the effects of some of which have been evaluated in preclinical trials, with promising results for inflammatory diseases and obesity.

New studies of probiotics in the treatment of various psychological states and autism are also beginning to be studied. The exact mechanism of how the microbiota influences gut-brain axis and behavior remains unknown, but there have been a few animal studies demonstrating the effects of probiotics to influence psychological states [132, 133]. In one such study, probiotics were tested as a delivery vehicle of neuroactive compounds due to their production of neurochemicals such as gamma-aminobutyric acid and other neurochemicals [134]. Similarly, emerging data have implied that a link between gut microbiome and autism may exist. Disruption of gut microbiota might promote the overproduction of neurotoxin-producing bacteria such as *Clostridium tetani*, which may contribute to autistic symptoms [135]. With better studies in humans, we await the results of appropriately designed placebo-controlled trials to further support the microbiome-gut-brain axis connection and identify a potential probiotic therapy for gastrointestinal and particular behavioral symptoms in human neurodevelopmental disorders.

CONCLUSIONS

The human gut microbiota plays an important role in human health, and the modulation of the gut microbiota may be used to treat and prevent an array of diseases. Prebiotics, probiotics, and synbiotics are appealing as preventive and therapeutic

agents for human medical disorders. Their efficacy depends on the etiology of the disease and the probiotic strain. Future research will focus on well-designed human trials as well as mechanisms of action of probiotics, to provide more data on different probiotics strains and mixtures. With new advances in research using metagenomics and bioinformatic tools, the field of prebiotics, probiotics, and synbiotics will continue to grow as these agents are being evaluated in the modulation of intestinal health.

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