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A comprehensive review on clinical outcome of probiotic and synbiotic therapy for inflammatory bowel diseases

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ABSTRACT

The composition of gut microflora and its metabolic activity are closely correlated with the host immune system, and the changes in the biometric of the microbiome lead to inflammatory diseases like inflammatory bowel disease. The supplementation of probiotics and synbiotic could indeed manipulate the microflora, which can be an alternative therapy for ulcerative colitis, and Crohn's disease. Several *in vitro*, *in vivo* and clinical studies for the initiation and maintenance of remission in patients with inflammatory bowel disease have been completed. Those studies evaluated the efficacy of many probiotic formulations, especially about VSL#3. Even though the clinical studies proved that almost all the probiotic interventions are safe and bring improvement to patients, some studies are deficient in sample size, proper controls, and follow-ups. This paper summarizes the possible mechanism of inflammatory bowel disease development, probiotics, the clinical outcome of probiotic and synbiotic interventions for ulcerative colitis and Crohn's disease, as well as the adverse effect of probiotic treatments.

1. Introduction

Gastrointestinal (GI) diseases are one of the severe hindrances of human health. The most reported GI diseases are inflammatory bowel disease (IBD) and intestinal neoplasia. Ulcerative colitis (UC) and Crohn's disease (CD) are the frequently described IBDs. The incidence of UC is more commonly reported than that of CD, and the frequency of UC cases are higher in developed countries. UK, Northern European and North American countries are reported for the high incidence of UC and CD[1–4]. Intestinal neoplasia is responsible for several deaths, particularly colorectal cancer, which is the third and fourth most common cause of morbidity and mortality, respectively[5–8].

The composition of gut microflora and its metabolic activity are closely correlated with the host immune system, and the changes in the biometric of the microbiome lead to inflammatory diseases like IBD. The functional food supplements are believed to sustain the health and to diminish the risk of developing diseases in human. Probiotics are live bacteria that have been revealed to exhibit beneficial effects on human health. The use of raw probiotic supplements and probiotic based foods like yogurt, fermented beverages and meats are gradually increased over the years. Several scientific reports revealed that the consumption of probiotic-based diet improved the health status of several diseases[9–11]. This paper mainly focuses on the beneficial clinical outcomes of probiotic supplements against IBD.

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2. Probiotics

Probiotics are well-defined as live microbes that exhibit health benefits on the host when administered in sufficient amounts[12]. The definition is also appropriate for fermented dairy products[12], dietary supplements, conventional foods, probiotic-containing drugs, probiotic mediated fermented foods, infant formula, medical foods, animal feed, non-oral probiotics and designer probiotics[13]. Probiotics are used from the ancient times and believed to have a history of usage for the past 10 000 years[14].

A microorganism is categorized as a probiotic based on the several regulations. The safety regulations for the use of probiotic are different among the countries. The probiotic based products are marketed as dietary supplements to healthy people in the USA[15]. The regulatory requirements for a probiotic-based drug and dietary supplement are different. A probiotic strain or combination of several probiotic strains that are proposed to treat any diseases or any ill health must undergo the regulatory process as a drug as per the Food and Drug Administration (FDA) regulations. Whereas regulatory process which is necessary for the drug is not required for the probiotic based products that are intended for use as food supplements, but it must stick with the guidelines of FDA's Center for Food Safety and Applied Nutrition[15].

Standard regulations have been developed to claim a microbial strain as probiotic by the experts from Food and Agriculture Organization of the United Nations and World Health Organization Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics. The guidelines endorse the following: (1) Strain identification using biochemical, and molecular methods to confirm the health benefits; (2) *In vitro* studies on evaluation of the possible mechanism of the probiotic effect; (3) The clinical trials to assess the health benefits on humans; (4) The biochemical and genetic safety assessments such as determination of drug resistance pattern, metabolic activities, side effects, production of any toxin, and no reports of pathogenicity[15–17].

The council also suggests third-party evaluation of the strain for its safety and stability. Some of the producers have evidence for probiotic effects and safety through small, randomized, controlled studies in human volunteers. Moreover, clinicians and medical prescriber must consider the scientific reports on the specified product and its beneficial effects before prescribing to people[15,17].

The strains of the genera *Bifidobacterium*, *Lactobacillus*, *Enterococcus*, *Streptococcus*, *Saccharomyces*, *Leuconostoc*, *Pediococcus*, and *Bacillus* are claimed as probiotics with proven health benefits. The bifidobacteria and lactic acid bacteria are commonly used probiotics while other bacteria and yeasts strains are also used as probiotics.

The probiotics were proved for several health benefits against antibiotic-associated diarrhea[18–20], travelers' diarrhea[21], functional constipation[22], urinary tract infections[23], infantile colics[24,25], ulcerative colitis[26], necrotizing enterocolitis[25], radiation-induced diarrhea[27], allergies[25,28], hypercholesterolemia[29]. It has also been proved that the administration of *Saccharomyces boulardii* (*S. boulardii*) along with antibiotics reduced the severity of *Clostridium difficile* infection[30,31], and the spores of *Bacillus subtilis* have been considered as probiotics to treat *Helicobacter pylori* infection and nosocomial bacteremia[32,33].

3. IBD

UC and CD are the most frequent types of IBD characterized by chronic intestinal inflammation. UC and CD differ in their histopathological signatures. An inflammatory reaction can be observed in UC with several blisters in the crypts and infiltration of eosinophils, plasma cells, and neutrophils that continuously affects the lining of the rectum and colon. In general, inflammation occurs in the same area in the case of UC with reduced disease period, and symptoms including abdominal pain, mucus discharge, rectal bleeding, diarrhea, and tenesmus. In the case of CD, the entire intestine may have affected by chronic inflammation with the physiognomies of scattered healthy tissues in between the affected area. The symptoms of CD are regular abdominal pain, fever, diarrhea, and weight loss. Most frequently, CD affects the colon and ileum[34–36].

The etiology of IBD is not understood completely. But, unhygienic lifestyle, pathogenic exposure, genetics, environmental factors like exposure to nonsteroidal anti-inflammatory drugs, tobacco, unhealthy diet (*e.g.*, fatty foods), and intestinal microbiota are the possible cause of IBD[36,37]. The composition of gut microbiota, which can alter the host immune response, is closely associated with the development of IBD[38–42]. The complete pathogenesis and molecular mechanism of IBD are not yet studied. The studies suggested that the IBD is the result of complex immune response against the intestinal microbiota[43]. The known mechanism of development of IBD has illustrated in Figure 1.

4. Probiotics and IBD

The incidence of IBD in a person may depend on the genetic aberrations, which stimulates the abnormal inflammatory response against intestinal microbiota. The intestinal microbiome is also responsible for the continuation of the inflammatory response, and it is proven that the intestinal bacteria can penetrate the mucosa and strengthen the intestinal epithelial inflammation[44–47].

The probiotics can change the microbial composition of the intestine, and it is believed that the probiotics support the growth of beneficial microbes. Thus, several probiotic based products and treatments are employed around the world. Nevertheless, the prescribed amount of probiotics and intervention strategies are varying based on the strain and the person who is consuming the product. It is necessary to have a minimal number of live bacterium, or combinations of bacteria with proven efficacy[48]. Many *in vivo* studies revealed the protective effects of several probiotic strains against IBD[49–52]. The present paper complied the results of a probiotic-based intervention to treat or abate the sternness of IBD (CD and UC) in human subjects.

The probiotic preparation, VSL#3, composed of viable cells of *Lactobacillus casei* (*L. casei*), *Streptococcus salivarius* subsp *thermophilus*, *Lactobacillus delbrueckii* subspecies *bulgaricus*, *Lactobacillus plantarum*, *Lactobacillus acidophilus* (*L. acidophilus*), *Bifidobacterium breve* (*B. breve*), *Bifidobacterium infantis*, and *Bifidobacterium longum* (*B. longum*). Several clinical studies were conducted in UC and CD patients to assess the protective nature of VSL#3. The studies proved that the supplementation of VSL#3

increased the remission rate and reduced the rate of relapse in UC patients, and also reduced the symptoms of the CD. TLR-2 expression, inflammatory cytokines, and IL-12p40 production were reduced, and IL-10 production was increased during VSL#3 intervention in UC patients. About 60% of UC disease activity index was reduced, and the endoscopic and histological scores were reduced by probiotic treatment. Moreover, VSL#3 supplementation increased the load of bifidobacteria, lactobacilli, and *Streptococcus salivarius* ssp. *thermophilus*. But, there were no changes in Bacteroides, clostridia, coliforms, total aerobic and anaerobic bacteria load. Over all, all the studies suggested that VSL#3 supplementation was safe, which not only reduced the expression level of inflammatory cytokines and the severity of both adult and pediatric active UC but also maintained the remission of UC[53-58].

UC patients were treated with sulphasalazine and glucocorticoid; then they were supplemented daily with 1.26 g of Bifico, a bifid triple viable capsule, for eight weeks. About 20% of patients exhibited the relapses after two months of study. The fecal lactobacilli and bifidobacteria load were increased. DNA binding property of NF-κB and NF-κB p65 expression was reduced. The expression level of anti-inflammatory cytokines was improved. The authors claimed that the Bifico was effective in prevention of the relapse in chronic UC[59]. UC patients were treated with salazosulphapyridine (3-4 g/d), or mesalazine (2 250-3 000 mg/d) for one month prior to the supplementation of bifidobacteria-fermented milk (BFM) (10 billion cells of *L. acidophilus* strain Yakult, *Bifidobacterium bifidum* strain Yakult, and *B. breve* strain Yakult per 100 mL) per day for 12 weeks. After 12 weeks of treatment, the clinical activity index was more reduced in BFM treated group than that of the placebo. BFM treated group showed the reduction in histological score and endoscopic activity index. The concentrations of fecal propionate, total short-chain fatty acid, and butyrate were increased upon BFM supplementation in UC patients[60].

Mild to moderate distal UC patients were provided with a commercial probiotic blend of *Bacillus mesentericus* TO-A (10 mg), *Clostridium butyricum* TO-A (10 mg), and *Enterococcus faecalis* T-110 (2 mg) per tablet, called BIO-THREE (9 tablets per day) for 4 weeks. The endoscopic findings and clinical symptoms were determined as UC disease activity index and the changes in the fecal microbiota was evaluated by terminal restriction fragment length polymorphism. The results suggested that about 45% of UC patients exhibited remission because of the intervention of BIO-THREE tablets, and the bifidobacterial load in feces was increased. The BIO-THREE was considered safe and effective for the treatment of UC[61]. Another recent report by Yoshimatsu *et al*[62] also claimed that the BIO-THREE was effective for maintaining remission in UC patients.

About 120 UC patients were divided into three groups and supplemented with probiotic (2×10^9 CFU of *B. longum*), prebiotic (8.0 g of psyllium per day), and synbiotic (2×10^9 CFU of *B. longum* and 8.0 g of psyllium per day), for 4 weeks, respectively and the health profile of the patients was evaluated. The results showed

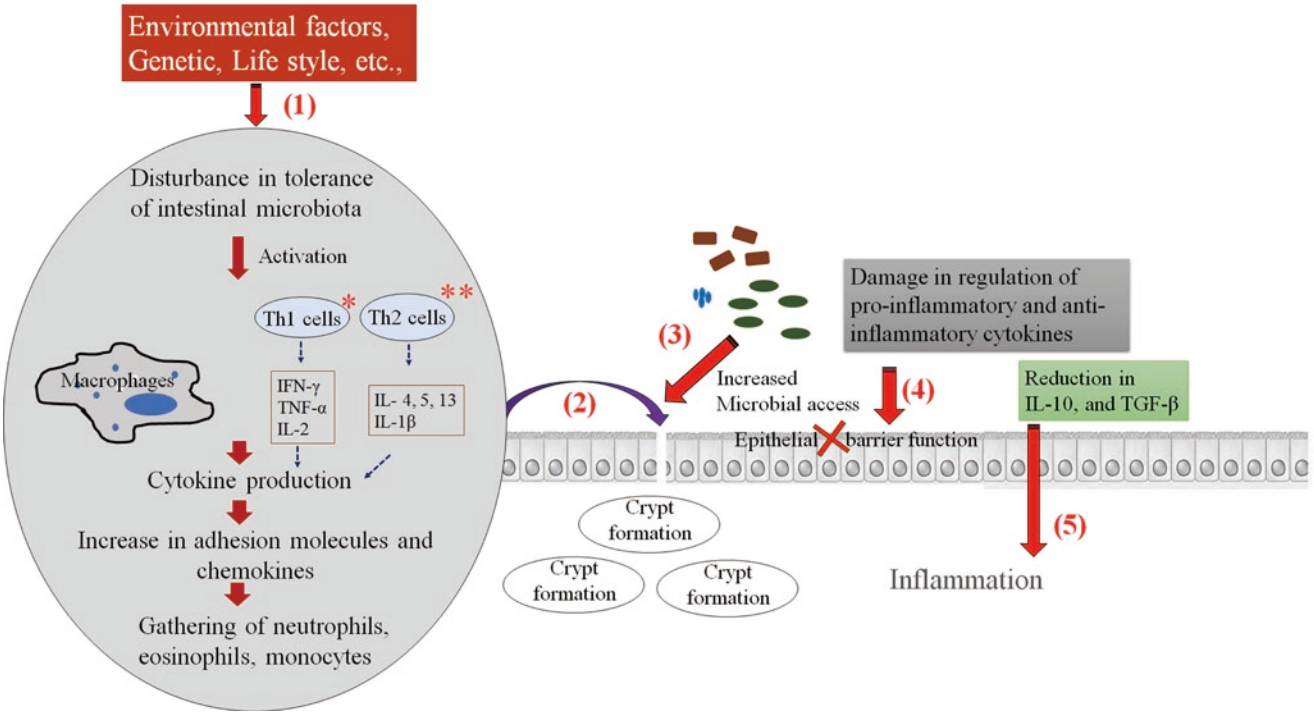

Figure 1. Schematic representation of molecular and cellular mechanism in the development of IBD.

(1) Factors including environmental factors, genetic factors, lifestyle *etc*. affect the intestinal microbiota, which further activate the immune cells and create the inflammatory machinery. (2) The inflammatory molecules cross the epithelial barrier and form crypt abscesses, (3) which facilitate the invasion of microbes that stimulate the inflammatory cytokines. (4) The fluctuations in the expression of pro-inflammatory and anti-inflammatory cytokines that leads to failure of epithelial barrier function. (5) Reduction of anti-inflammatory cytokines, which results in loss of tolerance to antigens of naïve microbiota, and facilitates the continuation of the inflammatory process. * In CD, T- helper 1 cells are involved and increase in IFN- γ , TNF- α , and IL-2 can be observed. Whereas, ** in UC, increased production of IL-4, IL-5, IL- 13 and IL-1 β was observed with the action of T- helper 2 cells.

that the probiotic intervention improved the emotional function and Inflammatory Bowel Disease Questionnaire scores, and prebiotic intervention improved bowel function and Inflammatory Bowel Disease Questionnaire scores. Whereas, the synbiotic intervention ameliorated the social and systemic functions, and Inflammatory Bowel Disease Questionnaire scores, and decreased the level of C-reactive protein. Collectively, the synbiotic intervention enhanced the life quality of UC patients, when compared to that of the probiotic and prebiotic supplements[63].

The supplementation of 2 400 mg per day of sulfasalazine, and *Lactobacillus delbruekii* and *Lactobacillus fermentum* (10 billion CFU per day) for eight weeks diminished the inflammation by reducing the leukocyte recruitment, myeloperoxidase activity, and expression level of NF-κB p65 and TNF-α in UC patients. Moreover, the reduction in fecal calprotectin level was observed in probiotic-treated UC patients. The supplementation of *Lactobacillus delbruekii* and *Lactobacillus fermentum* along with chemotherapy maintained the remission and prevented the relapse of UC[64]. Two capsules (thrice per day) of Probio-Tec AB-25 (a probiotic blend of equal concentration, 1.25×10^{10} CFU, of *Bifidobacterium animalis* subsp. *lactis* BB-12 and *L. acidophilus* LA-5, respectively) has been supplemented for 52 weeks to the patients with left-sided UC. The study results showed that about 25% of patients maintained remission after one year of treatment, and also average relapse period was extended in Probio-Tec AB-25 treated group. The study revealed that the Probio-Tec AB-25 was safe, and significantly protected the patients from UC recurrence[65].

D'Inca *et al*[66] explained the efficiency of intervention mode of probiotic for the treatment of UC. The UC patients were grouped into three (group 1, 2, and 3) and supplemented with 5-aminosalicylic acid (2.4 g per day), 5-aminosalicylic acid (2.4 per day) + oral *L. casei* DG (8×10^8 CFU twice a day), and 5-aminosalicylic acid (2.4 g per day) + Rectal administration of *L. casei* DG (8×10^8 CFU twice a day), respectively, for 8 weeks. The colonic microflora and the level of expression of TLR were not affected in the patients of 5-aminosalicylic acid, and 5-aminosalicylic acid + oral *L. casei* DG supplemented groups. Whereas, rectal administration of *L. casei* DG suppressed the IL-1β, and TLR-4 expression, and increased the IL-10 level. The reduction in *Enterobacteriaceae* and increase in *Lactobacillus* spp. have also been detected in group 3. The results proved that *L. casei* DG, as a potent probiotic, enhanced the mucosal immune system of UC patients. Another study by Oliva *et al*[67] proved that the rectal enema of *Lactobacillus reuteri* ATCC 55730 (10^{10} CFU per day) along with oral supplementation of 50 to 75 mg/kg/d of mesalazine could significantly decrease the clinical signs and histological scores. The level of IL-10 was increased, and the levels of IL-1β, IL-8, and TNF-α were found to be decreased. The results suggested that the rectal infusion of *Lactobacillus reuteri* was efficient to reduce the mucosal inflammation in pediatric UC.

Synbiotic, prepared with *B. breve* Yakult (10^9 CFU/g; 3 g per day) and galacto-oligosaccharide (GOS) (5.5 g per day), was supplemented to UC patients for one year, and the clinical status of UC, myeloperoxidase concentration, and fecal microbiota was assessed. The results showed that the level of myeloperoxidase and the colonoscopic index were improved. The fecal pH and fecal *Bacteroidaceae* count were reduced. The synbiotic preparation improved the clinical condition of UC patients[68].

UC patients were supplemented with increasing dose of Profermin®, a fermented oatmeal with lecithin, barley malt, *Lactobacillus plantarum* 299v ($\geqslant 10^8$ cells/mL), and water, for 24 weeks. The results suggested that about 46% of patients exhibited the significant reduction in Simple Clinical Colitis Activity Index, and the mean time taken to reach half the reduction in repeated-measure regression analysis score was 28 days. Moreover, the authors demanded that the Profermin® was harmless and could induce the remission of UC[69]. The intervention of single probiotic strain, *Bifidobacterium infantis* 35624, to UC patients improved the C-reactive protein level and decreased the expression of IL-6. It has been proved that *Bifidobacterium infantis* 35624 can diminish the systemic inflammation in UC patients[70].

The UC patients with severe pouchitis have been treated with 500 mg of metronidazole (thrice per day), and 500 mg of ciprofloxacin (twice per day) for four weeks, followed by multi-strain probiotic preparation, Ecologic 825 (*Bifidobacterium lactis* (W51 and W52), *Bifidobacterium bifidum* W23, *Lactococcus lactis* W19, *L. casei* W56, *Lactobacillus plantarum* W62, *Lactobacillus paracasei* W20, *Lactobacillus salivarius* W24 and *L. acidophilus* W22; 2.5×10^9 CFU/g; 3 g twice per day) for eight weeks. The Pouchitis Disease Activity Index was improved after treatment. The intestinal permeability level of the patients was evaluated with a representative strain of *Escherichia coli* (*E. coli*) K12, and the results suggested that *E. coli* K12 passage was reduced. The results revealed that Ecologic 825 intervention restored the mucosal barrier function in UC patients[71].

Petersen *et al*[72] studied the impact of the intervention of *E. coli* Nissle 1917 (100 mg per day for four days, and 200 mg per day until seven weeks) on the health status of UC patients along with prior standard medications (1 000 mg of ciprofloxacin per day for one week). The results suggested that *E. coli* Nissle was not suitable for the add-on treatment for UC along with antibiotics.

The intervention of *Clostridium butyricum* MIYAIRI (60 mg thrice per day) to UC patients for 24 months significantly suppressed the pouchitis development, and each group showed typical intestinal flora. The results suggested that *Clostridium butyricum* MIYAIRI can be a potent candidate for probiotic treatment[73]. A long-term (two years) intervention of two doses of Acronelle® (*Lactobacillus salivarius*, *L. acidophilus* and *Bifidobacterium bifidus* strain BGN4) along with a single dose of mesalazine (1 200 mg per day) to UC patients resulted in the reduction of clinical consequences of UC. The results also revealed that Acronelle® could be an alternative to steroid therapy for UC[74]. A sum of fifty-six patients with mild to moderate UC was treated with single probiotic strain, *B. longum* 536 (2×10^{11}–3×10^{11} cells per day), for eight weeks. About 63% of clinical remission was observed in the probiotic-treated group. The UC disease activity index score, endoscopic index, and Mayo sub-score were found to be reduced after the treatment. Overall, *B. longum* 536 intervention improved the health status of UC patients[75].

About five UC and fifteen CD patients were supplemented with the yogurt containing probiotic strains, *Lactobacillus reuteri* RC-14 (1×10^3 CFU) and *Lactobacillus rhamnosus* GR-1 (2×10^7 CFU) for 30 d. After 30 days of treatment, $CD4^+$ $CD25^{high}$ T cells proportion was increased, whereas the proportion of myeloid dendritic cells and TNF-α /IL-12 monocytes was reduced in both UC and DC patients. The follow-up study also suggested that the consumption of probiotic yogurt significantly suppressed the inflammation[76].

Shadnoush *et al*[77] also revealed the beneficial effect of probiotic

yogurt on UC and CD patients. About 250 g of yogurt containing probiotic strains (10^6 CFU/g of yogurt) namely, *Bifidobacterium* BB-12 and *L. acidophilus* LA-5 was supplemented daily to UC and CD patients for eight weeks. Stool samples were collected from the patients before and after the intervention, and the changes in microflora were analyzed by qPCR. The results showed that the mean numbers of *Lactobacillus*, and *Bifidobacterium* were significantly increased in the treatment group compared to placebo. Significant changes were not observed in weight, and body mass index of the patients.

Patients with CD in remission were treated with lyophilized cells of *S. boulardii*-17 (200 mg; 4×10^8 cells), magnesium stearate (2.4 mg), and sucrose (6 mg) per day for three months. At the end of the 3rd month, the lactulose/mannitol ratio was found to be reduced in the treatment group compared to that of the placebo group. The intestinal permeability was also improved upon treatment of CD patients. The study revealed that *S. boulardii* supplementation along with baseline therapy enhanced the intestinal permeability of CD patients in remission, but complete curing was not observed[78].

Vleggaar *et al*[79] studied the beneficial effects of probiotic preparation, Ecologic 641 (*Bifidobacterium bifidum*, *Lactococcus lactis*, *L. casei*, *Bifidobacterium lactis*, *Lactobacillus salivarius*, and *L. acidophilus*) on patients with primary sclerosing cholangitis and concurrent IBD. Fourteen patients were treated daily with 10^{10} cells of Ecologic 641 for three months and did the crossover after one month of the washout period. Significant changes was not observed between the treated and placebo groups in pruritus, fatigue, stool frequency, prothrombin, albumin and tested enzymes such as γ glutamyl transpeptidase, alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase. The study results proved that Ecologic 641 don't have any beneficial effect on patients with primary sclerosing cholangitis. Bourreille *et al*[80] reported that the supplementation of *S. boulardii* (1 g/d) for 52 weeks to CD patients does not influence the relapse and the concentration of C-reactive protein.

Clinical outcomes have been found to be improved in CD patients as a result of synbiotic (six gram of Synergy 1, and 2×10^{11} CFU of *B. longum*; twice a day) intervention for six months. The significant reduction in Crohns disease activity index and histological scores was observed. After synbiotic treatment, the expression of TNF-α was reduced, and the mucosal bifidobacteria level was found to be increased in CD patients[81].

Ahmed *et al*[82] investigated the impact of synbiotic on the colonic microflora of IBD patients. Both UC and CD patients were supplemented with three Trevis® capsules (each capsule contains 4×10^9 cells of *Bifidobacterium animalis* subsp. *lactis* BB-12®, *Streptococcus thermophilus* STY-31™, *Lactobacillus delbrueckii* subsp. *bulgaricus* LBY-27, and *L. acidophilus* LA-5®), and oligofructose (15 g per day) for one month. After treatment, the changes in the microbiota of the patients were assessed by terminal restriction fragment length polymorphism and qPCR. The results suggested that significant changes were not observed among the treated and placebo groups of both UC and CD patients. The authors claimed that the studied synbiotic supplementation does not affect the colonic microflora of IBD patients.

5. Adverse effect of probiotics

There are no reported significant adverse effects of the probiotic intervention on IBD patients. *B. longum* 536 supplementation caused a mild side effect (a dry cough) on one of the UC patients[75].

Though the probiotics are used for preventing, managing and treating several diseases which are common, some of the unwanted side effects like GI side effects, unwarranted immune stimulation, systemic infections, gene transfer, and lethal metabolic activities have been seen in some group of people, who have undergone the probiotic supplementation[83].

Several cases of fungemia, bacteremia, overt sepsis and endocarditis are associated with known probiotic strains namely *S. boulardii*, *L. casei*, *L. acidophilus*, *Lactobacillus* GG, *Bacillus subtilis*, *B. breve*, and *Lactobacillus rhamnosus*[84-96]. It has been reported that the probiotic intervention prompts the inflammatory response in the small bowel region, and causes D-lactic acidosis[97,98]. The possibilities of gene transfer among the intestinal bacteria, excess stimulation of both innate and adaptive immune system, and adverse effects in GI track have also been documented[83].

Recently, Brunser[99] reviewed the safety and risk of the use of probiotics, in particular for infants, and immune-compromised patients. The reports and clinicians claimed that the use of probiotics relies on birth, age and medical conditions of an individual, and it is important to convey the unpleasant effects of probiotic to the user.

6. Conclusion

The studies suggested that the intervention of multi-strain probiotic preparation or synbiotic preparation performed better than single strain therapy. Moreover, several studies were conducted with VSL#3 and proved that the VSL#3 was safe and recommended by many clinicians to support the remission of UC, and for maintenance therapy. Most of the clinical trials, except some recent studies, were conducted with a minimum number of patients or short treatment duration or no proper follow-up. Apart from the formulation of best probiotic or synbiotic preparation, dosage, duration, mode of intervention, and form of supplementation are playing a critical role in the outcome of a clinical trial. Overall, the present review suggested that probiotics are the healthier alternatives to conventional therapy or an adjuvant for standard therapy for IBD. Further, elaborated studies are required to figure out the potent probiotic strain or combinations to treat or control the IBD, and to maintain the remission.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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