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A Comprehensive Analysis of Efficacy and Safety of Probiotics in Inflammatory Bowel Disease

Feruza Abraamyan, Neeladri Misra

Sutter Roseville Medical Center, Roseville, California, USA
Email: fabraamyan@gmail.com

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Abstract

Introduction: Inflammatory bowel disease (IBD) affects approximately 7 million people worldwide. In the U.S. alone, per the CDC, 1.3% of adults, which is approximately 3,000,000 people, are diagnosed with inflammatory bowel disease-either, Crohn's disease, or ulcerative colitis. The estimated cost of treatment can be close to $23,000 annually, with treatment regimens comprising biologic agents and anti-inflammatory therapies. Probiotics have recently gathered interest as a low-cost additional therapy option that, in addition to the current regimen of IBD management, allows for reductions in rates of IBD flare-ups by significantly reducing the number of emergency room visits and avoiding the need to constantly escalate treatment by addition of biologic agents in achieving remission. **The Analysis Goal:** Our research project aimed to see if there was a significant difference in the addition of probiotics to standard therapy in inflammatory bowel disease by comparing existing research studies and trials. We analyzed RCTs published in PubMed to assess the efficacy and safety of probiotics in patients with IBD in preventing frequent disease flare-ups and reducing the cost of care. **Research Methods:** We did a comparative analysis of available RCTs using a PubMed search and included studies that researched the addition of probiotic strains in patients with IBD (ulcerative colitis and Crohn's disease). After reviewing the inclusion and exclusion criteria, the trials selected for analysis were reviewed by two independent reviewers. **Results:** We analyzed 21 RCTs, and 16 RCTs (76.2%) showed that probiotics are an effective therapy for IBD, inducing remission and reducing flare-up rates in patients on a standard treatment regimen. **Conclusion:** Probiotics given in combination with standard therapy in IBD are effective in decreasing disease activity rates and reducing remission rates. No significant adverse reactions to probiotics were noticed.

Keywords

Probiotics, Inflammatory Bowel Disease, Crohn's Disease, Ulcerative Colitis, Remission Rates

1. Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory condition that includes Crohn's Disease (CD) and Ulcerative Colitis (UC) [1]. Initially, IBD was associated with highly developed countries; however, currently, new cases are seen worldwide, including in Asia and Africa [2] [3]. According to the CDC data, in 2015 in the US, about 3 million adults were reported to be diagnosed with IBD. At the same time, about 7 million people worldwide have IBD, with an estimated cost of treatment being almost $23,000, according to the Crohn's and Colitis Foundation.

Genetics, immunological, and environmental factors combined with intestinal barrier disturbances are considered critical elements in the pathogenesis of IBD. Although the exact etiology of IBD remains unknown, research suggests that gut microbiome changes are considered one of the factors involved in disease progression: an altered immune response triggered by environmental factors targeting gut and gut microbiota in a genetically susceptible individual [4] [5] [6] [7]. At the same time, microbiome products and antigens affect the immune cells and the connection between the epithelial cells, leading to increased susceptibility to inflammation and gut permeability. However, it remains unclear if altered gut microbiome is a cause or a consequence of inflammation in IBD patients [8] [9].

Even though it's known that prebiotics act on specific bacterial populations and enhance their growth, probiotics are living microorganisms that benefit the host by modifying the intestinal microbiota. Different probiotic strains have been isolated from food culturing, including *Lactobacillus* species, *Bifidobacterium* species, non-pathogenic *E. coli*, *Saccharomyces boulardii, C. butyricum*, *Streptococcus salivarius*, and *Lactococcus lactis* [10]. If taken in addition to the primary therapy, probiotics can change the efficacy of specific drug therapies commonly used in treating patients with IBD, such as anti-tumor necrosis factor-α or steroids.

According to the Crohn's and Colitis Foundation, while the annual cost of healthcare is approximately 4 times higher for patients with IBD than for non-IBD patients, it keeps rising, with the most significant components being therapeutics (biologics, opioids, and steroids), comorbidities (anemia and psychiatric illness) and emergency room visits. The addition of probiotics to the standard regimen of IBD would allow for decreasing rates of IBD flare-ups, which in turn would lead to significantly reducing the cause associated with the addition of therapies to achieve remission in IBD.

The types and combinations of probiotic strains and whether probiotics should be supplemental or standalone therapy in patients with IBD remain controversial. The primary aim of our research study was to present a systematic review of available randomized controlled trials (RCTs) evaluating the types of strains, treatment courses, and outcomes in patients with IBD treated with probiotics.

Our review also aims to assess the efficacy and safety of probiotics in patients with IBD. This study was done to assess whether probiotics can be a low-cost addition to standard IBD therapy, with the goal of preventing frequent disease flare-ups and reducing the cost of care.

2. Research Methods

We performed a PubMed search on randomized controlled trial studies from 1997 to 2022, using the following keywords: Probiotics in Inflammatory Bowel Disease. The following criteria were used to perform the comparative analysis of the studies.

Inclusion criteria: All studies included adult patients with IBD 18 years old and above with preserved colon, oral administration of probiotics, RCTs that compared probiotics with placebo or any other non-probiotic intervention, and patients with and without maintenance therapy for IBD.

Exclusion criteria: Patients with prebiotic or symbiotic therapies; patients with subtotal/total colon or ileus removal; the study did not evaluate for objective clinical signs of disease activity or relapse rate; the study did not provide information about the bacterial strains included in probiotic, and the probiotic composition is not easily searchable online, probiotics as part of dairy produce-yogurt or kefir; probiotics not administered orally; the full text of the trial is not available online.

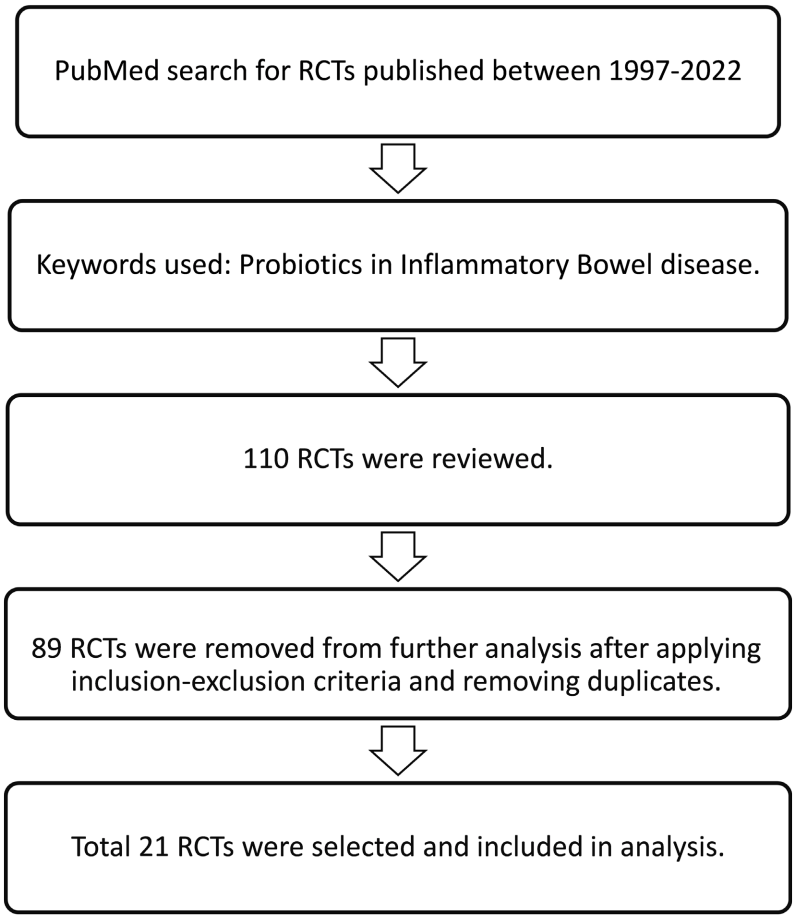
After discussion, both authors reviewed the studies independently and determined they were eligible if the criteria were met. The study inclusion and exclusion criteria and primary outcomes are outlined in the chart below, Figure 1.

3. Results

Out of 110 RCTs available in PubMed currently after applying keywords, 89 were removed from further analysis after the inclusion-exclusion criteria were used and duplicates were removed. Here, we reviewed data from the following probiotics (Table 1) and summarized the results of 21 selected RCTs, including 1948 patients in Table 2.

We examined the type and composition of bacterial strains included in probiotics, the treatment course, and the number of patients involved in the trial. We also evaluated outcomes such as disease activity index in treatment versus control groups, recurrence rates in treatment versus control groups, and adverse reactions.

Our analysis shows that out of 21 total RCTs—a total of 16 RCTs (76.2%) proved that probiotics are an effective therapy in patients with IBD to induce



Legend: RCT—Randomized Controlled Trials, IBD-Inflammatory Bowel Disease.

Figure 1. Summary of research method analysis.

Table 1. The name and bacterial strains of probiotics included in the analysis:

Name of the probiotic	Bacterial strains included in the composition of probiotic
Bifico	*Bifidobacterium longum*, *Lactobacillus acidophilus*, and *Enterococcus faecalis*
VSL#3	4 strains of *Lactobacillus*, 3 strains of *Bifidobacterium*, and 1 strain of *Streptococcus salivarius*
Bio-Three	*Streptococcus faecalis* T-110, *Clostridium butyricum* TO-A, and *Bacillus mesentericus* TO-A
Probio-Tec AB-25	*Lactobacillus* acidophilus La-5 and *Bifidobacterium animalis subsp*. lactis BB-12
BB536	*Bifidobacterium longum* 536
NA	*Saccharomyces boulardii*
NA	a combination of *Lactobacillus* and *Bifidobacterium* species
NA	a combination of *Lactobacillus salivarius*, *Lactobacillus acidophilus*, and *Bifidobacterium bifidus* strain BGN4
NA	*Lactobacillus rhamnosus* strain GG
NA	*Saccharomyces boulardii*
NA	*Escherichia coli* Nissle 1917

Legend: NA-not available.

Table 2. Summary of data from 21 RCTs selected and included in analysis.

Trial	Name of probiotic if available and include bacterial strains	Treatment regimen	Therapy outcomes	Adverse reactions
Fan H *et al.*, [11]	Bifico: *Bifidobacterium longum*, *Lactobacillus acidophilus* and *Enterococcus faecalis*	both treatment groups were on a pentasa (mesalamine extended action tablet) regimen; the treatment group was given additionally 2 probiotics tablets	CDAI/UCAI scores and recurrence rates were significantly lower in treatment group	no difference in adverse reactions between treatment groups
Bibiloni R *et al.*, [12]	VSL#3: 4 strains of *Lactobacillus*, 3 strains of *Bifidobacterium*, and 1 strain of *Streptococcus salivarius*	continued therapy for IBD was allowed if the dose was stable	achievement of remission or response rate in 77% of patients in treatment group	29% of patients: increased bloating; however, the side effect was not severe enough to stop the trial
Bourreille A *et al.*, [13]	*Saccharomyces boulardii*	probiotic versus placebo	no beneficial effect	diarrhea, arthralgia, constipation, and abdominal pain, 1 oral fungal infection
Agraib LM *et al.*, [14]	9 *Lactobacillus* and 5 *Bifidobacterium* species	probiotic versus placebo	significant induction of remission in the treatment group	NA
Palumbo VD, *et al.*, [15]	*Lactobacillus salivarius*, *Lactobacillus acidophilus*, and *Bifidobacterium bifidus* strain BGN4	mesalazine versus mesalazine + probiotic	significant induction of remission based on the treatment group	NA
Prantera C *et al.*, [16]	*Lactobacillus rhamnosus* strain GG	probiotic versus placebo	no significant differences between treatment groups	NA
Guslandi M *et al.*, [17]	*Saccharomyces boulardii*	mesalamine versus mesalamine+probiotic	significantly lower percentage of patients with clinical relapses in the treatment group	NA
Schultz M *et al.*, [18]	*Lactobacillus* GG	probiotic versus placebo	no benefit in inducing or maintaining remission in CD patients	NA
Huang M. *et al.*, [19]	Bifico: *Bifidobacterium longum*, *Lactobacillus acidophilus* and *Enterococcus faecalis*	mesalazine versus mesalazine+ probiotic	reduction in UCDAI score was more significant in the treatment group	the incidence rate of adverse reactions was lower in the treatment group
Yoshimatsu Y *et al.*, [20]	Bio-Three: *Streptococcus faecalis* T-110, *Clostridium butyricum* TO-A, and *Bacillus mesentericus* TO-A	continued therapy for IBD + probiotic versus placebo	significantly lower relapse and remission rates in the treatment group	NA
Tursi A *et al.*, [21]	VSL#3: 4 strains of *Lactobacillus*, 3 strains of *Bifidobacterium*, and 1 strain of *Streptococcus salivarius*	5-aminosalicylic acid (ASA) and/or immunosuppressants at stable doses+ probiotic versus placebo	higher decrease in UCDAI scores in the VSL#3 group than in the placebo group	dizziness, flu-like syndrome, abdominal bloating, and discomfort

Continued

Kruis W *et al.*, [22]	*E coli* Nissle 1917	probiotic versus mesalazine 500 mg three times daily	Probiotics are safe and effective in remission, equivalent to the gold standard mesalazine in patients with ulcerative colitis.	non-intestinal adverse events were viral infections (EcN 4.9%, mesalazine 4.2%), nausea (3.1%, 3.0%), and headache (1.9%, 0.6%)
Zocco MA *et al.*, [23]	*Lactobacillus* GG	*Lactobacillus* GG versus mesalazine versus *Lactobacillus* GG + mesalazine	probiotic considered to be effective and safe for maintaining remission	NA
Cui HH *et al.*, [24]	Bifico: *Bifidobacterium longum*, *Lactobacillus acidophilus* and *Enterococcus faecalis*	probiotic versus placebo	lower relapse rate in the probiotic group	NA
Sood A. *et al.*, [25]	VSL#3: 4 strains of *Lactobacillus*, 3 strains of *Bifidobacterium*, and 1 strain of *Streptococcus salivarius*	continued therapy for IBD + probiotic versus placebo	50% decrease in UCDAI at week 6 and clinical remission at week 12 in the treatment group	NA
Petersen AM *et al.*, [26]	Escherichia coli Nissle 1917	probiotic or placebo after pre-treatment with ciprofloxacin or placebo	no benefit in the use of E. coli Nissle as an add-on treatment to conventional therapies for active ulcerative colitis.	NA
Rembacken BJ *et al.*, [27]	*Escherichia coli* Nissle 1917	probiotic versus placebo	treatment with a non-pathogenic E. coli has an equivalent effect to mesalazine in maintaining remission of ulcerative colitis.	NA
Wildt S *et al.*, [28]	Probio-Tec AB-25: *Lactobacillus* acidophilus La-5 and *Bifidobacterium animalis* subsp. lactis BB-12	probiotic versus placebo	no significant clinical benefit	NA
Tamaki H *et al.*, [29]	BB536: *Bifidobacterium longum* 536	continued therapy for IBD + probiotic versus placebo	supplementation with BB536 was well tolerated and reduced UCDAI scores	no serious adverse events were reported
Kruis W *et al.*, [30]	*Escherichia coli* Nissle 1917	probiotic versus mesalazine	results of treatment with probiotics very equivalent to treatment with mesalazine	no serious adverse events were reported
Tursi A. *et al.*, [31]	VSL#3: 4 strains of *Lactobacillus*, 3 strains of *Bifidobacterium*, and 1 strain of *Streptococcus salivarius*	receive low-dose balsalazide plus VLS#3 versus medium-dose balsalazide alone versus mesalazine alone	balsalazide/VSL#3 combination was faster in obtaining remission than balsalazide alone or mesalazine	no serious adverse events were reported

Legend: CD-Crohn's Disease; CDAI-Crohn's Disease Activity Index; IBD-inflammatory bowel disease, NA-Not Applicable since data were not provided, UC-Ulcerative Colitis; UCAI-Ulcerative Colitis Activity Index.

remission rates. In the analysis, 13 out of 16 RCTs (61.9%) showed decreased disease activity scores or recurrence rates in probiotic versus placebo groups. In these studies, the probiotics used were: Bifico: *Bifidobacterium longum*, *Lactobacillus acidophilus*, and *Enterococcus faecalis* (4 studies); VSL#3: four strains of *Lactobacillus*, three strains of *Bifidobacterium*, and one strain of *Streptococcus salivarius subsp*. Thermophilus (3 studies); a combination of *Lactobacillus* and *Bifidobacterium* species (2 studies); *Saccharomyces boulardii* (1 study); Bio-Three: *Streptococcus faecalis* T-110, *Clostridium butyricum* TO-A, and Bacillus mesentericus TO-A (1 study); *Lactobacillus* GG (1 study); BB536: *Bifidobacterium longum* 536 (1 study).

Out of 16 studies with the beneficial effect of probiotics in the treatment group, in 10 studies, 62.5% of patients continued their standard treatment regimen for IBD as long as medication doses were stable and probiotics were given as supplemental therapy. At the same time, no significant adverse reactions to probiotics were noticed.

2 studies out of 16 RCTs (9.5%) showed that the *E. coli* Nissle 1917 probiotic is equivalent in maintaining remission to the gold standard of treatment with mesalazine in patients with ulcerative colitis, and 1 study out of 16 RCTs (4.8%) showed that the balsalazide/VSL#3 combination was faster in obtaining remission than balsalazide alone or mesalazine.

5 studies out of 21 RCTs included in our analysis (23.8%) showed no significant clinical benefit from probiotic therapy.

4. Discussion

Over 1 million residents in the USA and 2.5 million in Europe are estimated to have IBD, with substantial costs for health care, not counting the cost of altered quality of life [32]. Recent advances in next-generation sequencing technology have identified alteration of the composition and function of the gut microbiota in patients with IBD, called dysbiosis. Clinical and experimental data suggest that dysbiosis may play a pivotal role in the pathogenesis of IBD [33], prompting the initiation of probiotics in patients with IBD.

In our analysis, we searched and analyzed available RCTs published in PubMed to assess the efficacy and safety of probiotics for the induction and maintenance of relapse rates in patients with IBD and to decrease them. According to our analysis, the vast majority of RCTs concluded that probiotics are an effective therapy to decrease remission rates in patients with IBD.

The mechanism of how probiotics can be effective in patients with IBD comes from animal studies. For example, experiments involving genetically engineered animals raised in germ-free environments showed an absence of intestinal inflammation. Interestingly, in a laboratory interleukin (IL)-10 deficient mice, IBD-like intestinal inflammation does not occur without an intestinal bacterial flora. However, an inflammatory response occurs after exposure to the standard microbial environment [34] [35]. In humans, the areas most affected by IBD are

gut regions characterized by the highest bacterial populations, such as the terminal ileum and colon. At the same time, antibiotics are helpful in decreasing the severity of active inflammation in patients with IBD [36] [37].

Recent studies have revealed that patients with IBD have decreased concentrations of *bifidobacterium* and *lactobacillus* and a significant increase in pathogenic and potentially harmful enterobacteria. The mechanisms through which probiotics benefit IBD patients can be explained in the following ways [36]:

1) Firstly, probiotics inhibit the attachment and invasion of enterotoxigenic and enteropathogenic bacteria to the gut epithelium by competing with microbial pathogens for the limited number of receptors on the surface of epithelia [38].

2) Secondly, probiotics enhance epithelial tight junctions and barrier function by activating the antiapoptotic and inhibiting the activation of the pro-apoptotic pathways, which improves intestinal epithelial cells' survival in environments rich in pro-apoptotic cytokines [39].

3) Thirdly, probiotics modulate the immune response in intestinal epithelial and mucosal immune cells by downregulating the expression or secretion of various proinflammatory cytokines, such as TNFα, IL1β, interferon-gamma, nitric oxide synthase, and matrix metalloproteinase [40] [41] [42] [43] [44].

4) Lastly, probiotics stimulate the secretion of antimicrobial substances by upregulating defensins, which are impaired in Crohn's disease [36].

While our analysis showed that probiotics could be an effective supplemental therapy to maintain remission in patients with IBD, we looked deeper into which bacterial strains showed the best outcomes in decreasing order:

VSL#3: Four strains of *Lactobacillus*, three strains of *Bifidobacterium*, and one strain of *Streptococcus salivarius* given as supplemental therapy in 4 studies showed a higher decrease in UCDAI scores in the VSL#3 group than in the placebo group.

Bifico: *Bifidobacterium*, *Lactobacillus* acidophilus, and *Enterococcus faecalis* in 3 studies showed decreased CDAI/UCAI scores and recurrence rates in the treatment group. While CDAI/UCAI scoring systems are built based on such criteria as stomachache, diarrhea, gross blood in stool, fecal incontinence, abdominal hyperalgesia, abdominal mass, and the number of complications, patients in the treatment group reported improvement in their symptoms after initiation of the probiotics.

Bio-Three probiotics containing *Streptococcus faecalis* T-110, *Clostridium butyricum* TO-A, and *Bacillus mesentericus* TO-A showed significantly lower relapse and remission rates in the treatment group in 1 RCT.

Lactobacillus and *Bifidobacterium* species combo in 2 studies showed significant remission induction in the treatment group, and in 1 study—no significant clinical benefit [28].

In 3 trials, the *E. coli* Nissle 1917 probiotic was safe and effective in maintaining remission equivalent to the gold standard mesalazine in patients with ulcerative colitis. However, in 1 trial, there was no benefit in using *E. coli* Nissle as an add-on treatment to conventional therapies for active ulcerative colitis.

Saccharomyces boulardii alone did not show any beneficial effect in one study, but in another, it significantly lowered the percentage of patients with clinical relapses in the treatment group.

Lactobacillus alone in 2 trials didn't show significant differences between treatment groups; however, in one trial, probiotics were considered effective and safe for remission.

BB536: *Bifidobacterium longum* 536 alone in 1 trial showed that probiotic supplementation was well tolerated and reduced UCDAI scores.

In other words, probiotics administered with *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, or *Enterococcus* species show the best outcomes in decreasing disease activity and reducing remission rates, which correlates with most available literature data.

Our analysis had such limitations as not all trials had appropriate randomization of patients based on disease activity scores, laboratory and endoscopy findings before initiation of trial; sex and race of patients involved in RCTs varied broadly across studies, while some trials included patients on the continued regimen for IBD with probiotic being a supplemental therapy, other trials evaluated patients being only on monotherapy with probiotics or placebo number of patients; no gold equivocal stratified system accessing outcomes in patients with IBD and UC, with some studies using the short or full version of Ulcerative Colitis/Crohn's Disease Activity Index (UCAI/CDAI) or Mayo systems, not using them at all or using another scoring system; objective evaluation of laboratory data and gut mucosa with endoscopy after trial completion was not performed in all trials as well; our analysis only included RCTs from PubMed.

It is essential to notice that in RCTs where probiotics showed a positive effect on decreasing relapse rates, they were given as supplemental therapy to conventional standard therapy for IBD treatment. That confirms that probiotics are not a stand-alone treatment for IBD, but they have proven potential to prolong remission and decrease relapse rates in patients with IBD.

The average admission cost for IBD patients varies significantly depending on factors such as the severity of the condition, the type of treatment required, and the duration of hospitalization. In the United States, for example, the average cost of hospital admission for IBD can range from several thousand to tens of thousands of dollars, depending on whether the patient requires surgery, specialized treatments, or prolonged hospital stays.

The opportunity to decrease relapse rate by adding probiotics would allow for avoiding hospitalization in patients with IBD, thus saving significant amounts of dollars for the patient and the healthcare system in general.

While probiotic therapy is safe and effective in managing patients with IBD, the absence of significant adverse reactions makes it a desirable supplement to decrease disease activity, prolong remission, and improve outcomes. However, we are advocating for the need to perform and analyze more standardized randomized controlled studies assessing the role of probiotics in patients with IBD.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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