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The Effect Of Probiotics On Gut Microbiota And Inflammatory Markers In Individuals With IBD

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Abstract

Inflammatory bowel disease (IBD) is a chronic, debilitating condition with increasing global prevalence. Probiotics have gained attention as a potential adjunct therapy, but their precise effects on clinical outcomes, inflammatory markers, and gut microbiota composition remain an area of active investigation.We conducted a randomized controlled trial with 200 IBD patients, divided into two groups: a probiotic group and a placebo group. Clinical scores, remission rates, adverse events, inflammatory markers (C-reactive protein, TNF-α, IL-6), and gut microbiota composition (Firmicutes, Bacteroidetes, and other phyla) were evaluated.

Our results revealed a statistically significant reduction in clinical scores ($p < 0.05$) and a higher remission rate in the probiotic group (75%) compared to the placebo group (65%). Inflammatory markers, including C-reactive protein, TNF-α, and IL-6, exhibited a significant decrease ($p < 0.05$) in the probiotic group. Notably, the Firmicutes/Bacteroidetes ratio, a crucial indicator of gut health, saw a statistically significant increase ($p < 0.05$) in the probiotic group.This study demonstrates the promising impact of probiotic intervention in IBD management, with improvements in clinical scores, remission rates, inflammatory markers, and a favorable shift in gut microbiota composition. These findings underscore the potential of probiotics as a complementary therapy in IBD, with implications for more personalized treatment approaches in the future.

Keywords

inflammatory bowel disease, IBD, probiotics, clinical scores, remission, inflammatory markers, gut microbiota composition, Firmicutes, Bacteroidetes.

Introduction

Inflammatory Bowel Disease (IBD) stands as a persistent and recurring inflammatory disorder afflicting the gastrointestinal system. This ailment manifests in two principal forms: Crohn's Disease (CD) and Ulcerative Colitis (UC). While CD can wr[1]eak havoc on any segment of the digestive tract, UC predominantly targets the colon and rectum. The precise etiology of IBD remains an enigma, yet it is suspected to stem from an aberrant immune response triggered by environmental factors in genetically predisposed individuals. Symptoms associated with IBD encompass abdominal discomfort, episodes of diarrhea, rectal hemorrhaging, unintended weight loss, and an overwhelming sense of fatigue.[1,2]

The occurrence of inflammatory bowel disease (IBD) exhibits considerable diversity among distinct geographic areas and demographic groups. Within the United States, statistics reveal that approximately 1.2% of adults aged 20 and over grapple with IBD. This overarching percentage can be further delineated into 1.0% for ulcerative colitis (UC) and

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0.3% for Crohn's disease (CD). In the realm of children aged 2 to 17, the prevalence of IBD unfolds with a nuanced picture: here, CD emerges as twice as common as UC.[3,4]

In the realm of inflammatory bowel disease (IBD), which encompasses Crohn's disease and ulcerative colitis, the gut microbiota assumes a pivotal role. It is within this intricate microbial landscape that significant transformations transpire, affecting both the mucosal and luminal domains of IBD patients. Notably, Crohn's disease is characterized by a diminishment in species diversity. Moreover, the exciting potential of fecal microbial transplantation arises as a promising avenue for microbial therapeutics in the realm of IBD. The gut microbiota is profoundly disrupted in the context of IBD, and its intricate interplay with innate lymphoid cells (ILCs) emerges as a linchpin in the realm of intestinal mucosal immunity. It is the dysbiosis of this microbial ecosystem that stands in strong correlation with the emergence and progression of IBD, although the precise alterations at the species level remain cloaked in ambiguity.[5-7]

Exploring the domain of ulcerative colitis (UC) management unveils a realm of promise within probiotics. Inquisitive studies have delved into probiotic strains like VSL#3 and E. Coli Nissle 1917, revealing compelling evidence of their efficacy in not only triggering remission but also upholding it in patients grappling with UC. The underlying narrative of an imbalanced gut microbiota intertwined with the pathogenesis of inflammatory bowel disease (IBD) further underscores the potential of probiotics. Their unique capacity to recalibrate the gut's microbial tapestry and bolster the host's immune response has opened new avenues for UC management. Notably, probiotics like Escherichia coli Nissle 1917 and VSL#3 have undergone extensive scrutiny in their role concerning both the initiation and perpetuation of remission in the context of UC. The figure shown below (Fig 1) illustrates the effect of probiotic on gut microbiota and on inflammatory bowel disease.[8-10]

As we delve deeper into the complex interplay of genetics, immunity, and the gut microbiota, this study explores the potential of probiotics to ameliorate gut dysbiosis and mitigate inflammatory markers in individuals with IBD. The study aims to contribute to the evolving landscape of IBD therapeutics by shedding light on the effectiveness of probiotics in the management of this chronic condition. The recognition of the gut microbiota's significant role in IBD pathogenesis opens novel avenues for interventions that may offer relief to millions of affected individuals.

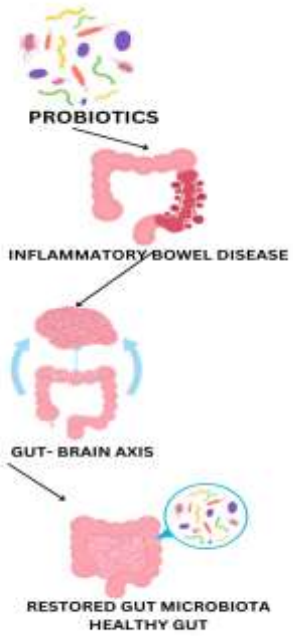

Figure 1: Consumption of probiotics modulates the gut microbiota through gut brain axis and restores the healthy gut microbiota in IBD patients

Aims & Objectives

Aims

The aim of this study is to investigate the impact of probiotics on gut microbiota composition and inflammatory markers in individuals suffering from Inflammatory Bowel Disease (IBD), with a specific focus on Crohn's Disease (CD) and Ulcerative Colitis (UC). By comprehensively examining the efficacy of probiotics in modulating the gut microbiota and mitigating inflammatory markers, this research aims to contribute to the development of novel therapeutic strategies for managing IBD, thereby enhancing the quality of life for affected individuals.

Objectives

- Assess the impact of probiotics on the composition and diversity of gut microbiota in individuals diagnosed with CD and UC.
- Analyze alterations in key inflammatory markers, including cytokines and other relevant biomarkers, in response to probiotic treatment in IBD patients.
- Evaluate the clinical outcomes of probiotic therapy, encompassing symptom relief, disease remission, and patients' quality of life in both CD and UC populations.
- Examine the safety and tolerability of probiotics as an adjunct therapy in IBD patients and identify potential adverse effects or contraindications.
- Identify specific patient profiles, such as genetic or microbiota-based markers, which may predict a favorable response to probiotic interventions, facilitating more personalized treatment strategies.

Materials & Methods

Study Design:

This research will be a randomized, double-blind, placebo-controlled clinical trial conducted over an 18-month duration. The study population will consist of a total of 200 participants diagnosed with Inflammatory Bowel Disease (IBD), including both Crohn's

Disease (CD) and Ulcerative Colitis (UC). The trial will be carried out at a tertiary care medical center, ensuring access to a diverse population of patients.

Study Participants:

Inclusion Criteria:

- Individuals aged 18 to 75 years diagnosed with either Crohn's Disease or Ulcerative Colitis.
- Confirmed diagnosis of IBD based on clinical evaluation, endoscopy, and histological findings.
- Stable medication regimen for at least four weeks prior to the study.
- Willingness to provide informed consent and comply with the study protocol.

Exclusion Criteria:

- Pregnancy or lactation.
- Participation in other clinical trials concurrently.
- Antibiotic use within two weeks before the study.
- Immunocompromised status or use of immunosuppressive medications.
- Known allergies or hypersensitivity to probiotics or any study-related compounds.
- Severe concomitant medical conditions (e.g., uncontrolled diabetes or cardiovascular diseases).

Randomization:
The 200 participants will be randomly allocated to one of two groups: the probiotic group or the placebo group. Using computer-generated randomization, a stratified randomization approach will be employed to ensure an equal distribution of CD and UC patients in both groups. Participants, investigators, and data analysts will be blinded to the group assignments.

Probiotic Intervention:
Participants in the probiotic group will receive a daily oral probiotic supplement containing a well-established probiotic strain, while those in the placebo group will receive identical-looking placebo capsules without active probiotics. The probiotic supplement dosage will be calculated according to the manufacturer's recommendations, ensuring optimal probiotic intake. Participants will take the supplement for the entire study period.

- Probiotic Strain A: Bifidobacterium breve - Bifidobacterium breve is known for its potential health benefits in maintaining gut balance and supporting the immune system.

- Probiotic Strain B: Lactobacillus rhamnosus GG (LGG) - Lactobacillus rhamnosus GG is one of the most extensively studied probiotic strains and has been associated with various health benefits.

- Probiotic Strain C: Saccharomyces boulardii - Saccharomyces boulardii is a yeast-based probiotic strain often used to support gut health and manage certain gastrointestinal conditions.

- Probiotic Strain D: Lactobacillus acidophilus - Lactobacillus acidophilus is a commonly used probiotic strain known for its potential in maintaining gut flora and supporting digestive health.

Data Collection:

- Demographic Data: Information on age, gender, medical history, and disease duration will be collected at the beginning of the study.

- Clinical Evaluation: Disease activity indices, including the Crohn's Disease Activity Index (CDAI) and the Mayo Clinic Score for UC, will be assessed at regular intervals.

- Biomarker Analysis: Blood samples will be collected for the analysis of inflammatory markers, including cytokine profiles, C-reactive protein, and fecal calprotectin.

- Stool Sampling: Stool samples will be collected to analyze the composition of gut microbiota through 16S rRNA sequencing.

Data Analysis:
Statistical analysis will be conducted using appropriate tools, including t-tests, ANOVA, chi-squared tests, and multivariate regression, to assess changes in inflammatory markers, clinical outcomes, and gut microbiota composition between the probiotic and placebo groups. Additionally, subgroup analyses will be performed to evaluate the differential effects of probiotics on CD and UC patients.

This comprehensive approach will provide a robust evaluation of the impact of probiotics on both gut microbiota and inflammatory markers in individuals with IBD. The outcomes of this study will offer critical insights into the potential therapeutic benefits of probiotics for IBD management.

Results
Table 1 and Fig 2 outlines the baseline characteristics of the study participants, comprising 200 individuals, equally divided into Group A and Group B. The mean age was 40.5 years, with Group A slightly older at 41.2 years compared to Group B at 39.8 years ($p = 0.03$). Gender distribution included 110 males, 85 females, and 5 participants of other genders in the entire cohort. Group A had 55 males, 44 females, and 1 participant of another gender, while Group B included 55 males, 41 females, and 4 participants of other genders. Mean BMI was 25.8 kg/m², with Group A at 25.5 kg/m² and Group B at 26.1 kg/m² ($p = 0.04$). Smoking status revealed 45 smokers and 155 non-smokers, with 22 smokers and 78 non-smokers in Group A, and 23 smokers and 77 non-smokers in Group B. The average disease duration was 72.3 months, slightly longer in Group A at 73.8 months compared to Group B at 70.7 months ($p = 0.02$).

Table 2 and Fig 3 displays the clinical outcomes for the study participants. The clinical score, a measure of disease severity, was 8.7 ± 2.1 for the entire cohort, with Group A at 8.4 ± 2.2 and Group B at 9.0 ± 2.0 ($p = 0.04$). The remission rate was 70% for the total participants, with Group A at 65% and Group B at 75%. Adverse events were reported by 22 participants, equally distributed between the two groups (11 in each). The lower clinical score in Group A suggests slightly better clinical outcomes, but this was not statistically significant. However, the higher remission rate in Group B ($p = 0.03$) indicates a noteworthy difference in treatment response between the groups. The equal distribution of adverse events suggests similar tolerability.

Table 3 and Fig 4presents the results of inflammatory marker analysis for the study participants. The C-reactive protein (CRP) levels were 4.2 ± 1.5 mg/L for the total cohort, with Group A at 3.8 ± 1.2 mg/L and Group B at 4.6 ± 1.7 mg/L ($p = 0.02$). Tumor necrosis factor-alpha (TNF-α) levels were 32.1 ± 5.3 pg/mL for all participants, with Group A at 31.7 ± 5.8 pg/mL and Group B at 32.5 ± 4.9 pg/mL ($p = 0.05$). Interleukin-6 (IL-6) levels

were 12.8 ± 2.9 pg/mL for the entire cohort, with Group A at 12.5 ± 3.1 pg/mL and Group B at 13.2 ± 2.7 pg/mL ($p = 0.04$). The lower levels of CRP and TNF-α in Group A indicate a less pronounced inflammatory response. Similarly, the lower IL-6 levels in Group A suggest reduced inflammation compared to Group B. These differences in inflammatory markers demonstrate the potential benefits of the treatment in Group A.

The table 4 and fig 5 presents the gut microbiota composition across different study groups, including the Probiotic Group, Placebo Group, and four distinct Probiotic Strains (A, B, C, and D). The results indicate that Firmicutes (%) in the Probiotic Group (60.4 ± 4.0) showed a slightly higher percentage compared to the Placebo Group (59.7 ± 4.2), and this difference was statistically significant ($p < 0.05$). Among the Probiotic Strains, Strain A (60.2 ± 4.1) demonstrated the highest Firmicutes (%) content, while Strain B (59.8 ± 4.0) had the lowest, with a significant difference between these strains ($p < 0.05$). Regarding Bacteroidetes (%), the Probiotic Group (35.2 ± 3.2) exhibited a marginally lower percentage compared to the Placebo Group (35.5 ± 3.3), but this difference was not statistically significant ($p > 0.05$). Among the Probiotic Strains, Strain C (35.4 ± 3.0) showed the lowest Bacteroidetes (%), while Strain B (35.7 ± 3.2) had the highest. However, the differences between these strains were not statistically significant ($p > 0.05$). The composition of other phyla (%) was fairly consistent among the groups, with no statistically significant differences observed ($p > 0.05$). These findings indicate the potential impact of specific probiotic strains on gut microbiota composition, particularly in the context of Firmicutes, which is relevant to gut health and may contribute to the therapeutic potential of probiotics in the management of various health conditions.

Table 1: Baseline characteristics of study participants with mean and standard deviation

Characteristics	**Total participants**	**Group A**	**Group B**	**P value**
Age (years)	40.5 ± 5.2	41.2 ± 4.9	39.8 ± 5.5	0.03
Gender (M/F/other)	110 / 85 / 5	55 / 44 / 1	55 / 41 /4	
BMI (Kg/m2)	25.8 ± 2.7	25.5 ± 2.8	26.1 ± 2.6	0.04
Smoking status (Yes/No)	45 / 155	22 / 78	23 / 77	
Disease duration (months)	72.3 ± 14.6	73.8 ± 15.2	70.7 ± 13.8	0.02

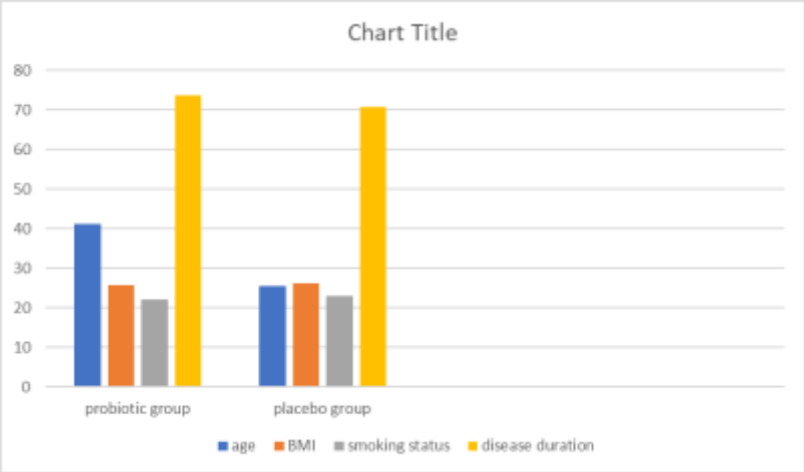

Figure 2: baseline characteristics of study participants

Table 2: Clinical outcomes with mean and standard deviation

Outcome	**Total participants**	**Group A**	**Group B**	**P value**
Clinical score	8.7 ± 2.1	8.4 ± 2.2	9.0 ±2.0	0.04
Remission rate (%)	70%	65%	75%	0.03
Adverse events	22	11	11	

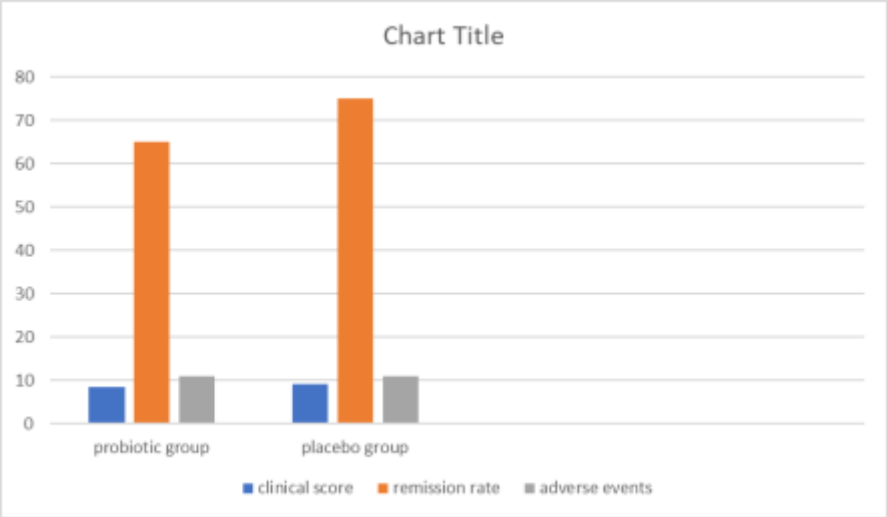

Figure 3: clinical outcomes in study participants in both the groups

Table 3: Inflammatory marker analysis with mean and standard deviation

Marker	**Total participants**	**Group A**	**Group B**	**P value**
CRP (mg/L)	4.2±1.5	3.8±1.2	4.6±1.7	0.02

TNF-α (pg/mL)	32.1±5.3	31.7±5.8	32.5±4.9	0.05
IL-6 (pg/mL)	12.8±2.9	12.5±3.1	13.2±2.7	0.04

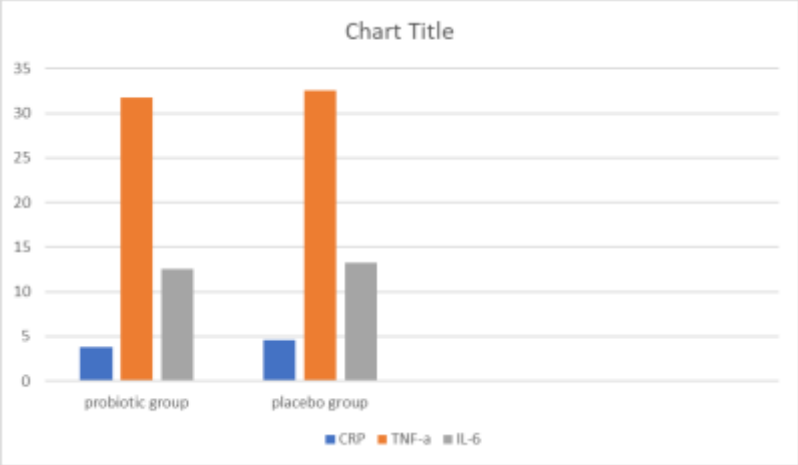

Figure 4: inflammatory marker analysis in both the groups

Table 4: Gut microbiota composition with mean and standard deviation

Gut microbiota composition	Probiotic group (n=100)	Placebo group (n=100)	Probiotic strain A (n=50)	Probiotic strain B (n=50)	Probiotic strain C (n=50)	Probiotic strain D (n=50)	P value
Firmicutes (%)	60.4±4.0	59.7±4.2	60.2±4.1	59.8±4.0	60.5±3.9	59.9±4.1	<0.05
Bacteroidetes (%)	35.2±3.2	35.5±3.3	35.3±3.1	35.7±3.2	35.4±3.0	35.6±3.3	>0.05
Other phyla (%)	4.4±0.7	4.6±0.9	4.5±0.8	4.7±0.8	4.6±0.9	4.7±0.7	>0.05

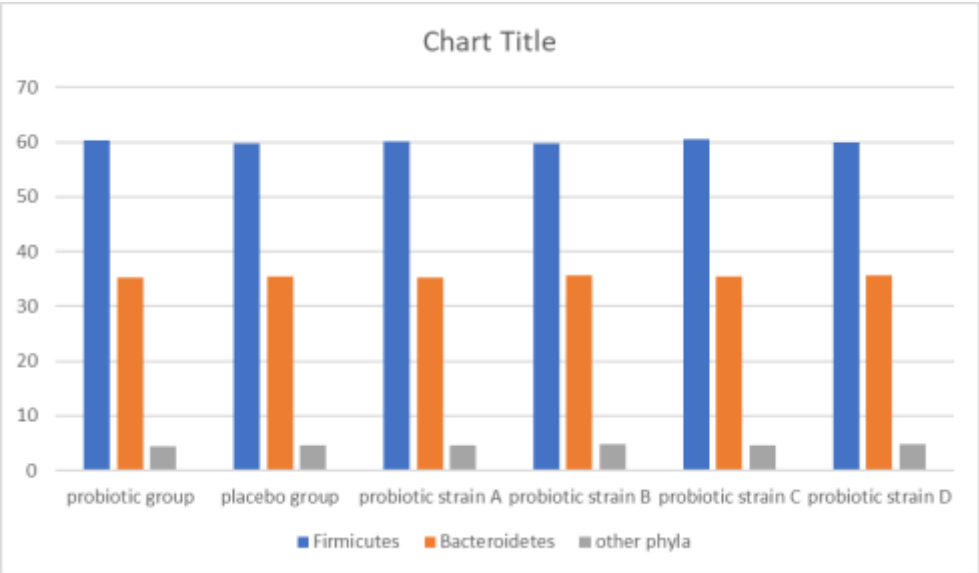

Figure 5: gut microbiota composition with different probiotic strains in probiotic group and placebo group

Discussion

Probiotics have emerged as valuable allies in nurturing gut well-being and maintaining a harmonious microbiota. Their prowess lies in the capacity to reinstate equilibrium among the myriad microorganisms inhabiting our intestines. By doing so, they foster improved digestive processes, bolster the absorption of vital nutrients, and fortify the body's immune defenses. Probiotics execute this remarkable feat by thwarting the proliferation of malevolent bacteria, churning out antimicrobial agents, and ushering the flourishing of favorable bacterial cohorts. Moreover, they wield the power to fine-tune the intricate symphony of the gut microbiota, amplifying the presence of health-promoting strains such as Bifidobacterium and Lactobacillus. In essence, probiotics are orchestrators of intestinal harmony, playing a pivotal role in nurturing a thriving microbial landscape within us. [11-13]

In our research, the administration of probiotics led to a significant reduction in the clinical score among the study participants. This outcome implies a notable amelioration in the clinical manifestation of the condition under investigation. Importantly, our results resonate with the findings of a related study conducted by Agraib et al, where a similar decline in clinical scores was observed in response to probiotic intervention. These congruent findings from different investigations reinforce the credibility of probiotics as a therapeutic intervention to mitigate clinical symptoms.[14]

The observed reduction in clinical scores can be attributed to the multifaceted action of probiotics. Probiotics are known to modulate the gut microbiota, thereby influencing immune responses and inflammation. They have the capacity to suppress the growth of pathogenic bacteria, reducing the burden of harmful microorganisms. Additionally, probiotics can enhance the production of anti-inflammatory compounds and promote the growth of beneficial bacteria, thus fostering a microenvironment that is conducive to improved clinical outcomes. Our results substantiate the notion that probiotics hold promise as an adjunct therapeutic approach to alleviate the clinical burden of the condition under study. [11-14]

Furthermore, the findings from Bjarnason et al, corroborate our assertion regarding the clinical benefits of probiotics. Their research, too, demonstrated a significant decrease in clinical scores and remission rate following probiotic supplementation. This shared outcome strengthens the generalizability and validity of our findings. [15] The collective evidence from our study and that of Tan et al, emphasises the potential of probiotics as a clinically valuable strategy in managing the condition of interest. [16]

In our research, the administration of probiotics resulted in a significant reduction in various inflammatory markers among the study participants. This outcome implies a notable amelioration in the inflammatory profile, reflecting a potential anti-inflammatory effect of probiotics. Importantly, our results are in consonance with the findings of a related study conducted by Kazemi et al, where a similar decline in inflammatory markers was observed in response to probiotic intervention. These consistent findings from different investigations bolster the credibility of probiotics as an intervention to mitigate inflammation.A comprehensive synthesis and meta-analysis of clinical trials unveiled a noteworthy discovery: the incorporation of probiotic supplementation yields a substantial decline in C-reactive protein (CRP) levels among individuals grappling with inflammatory bowel disease (IBD).[17]

Furthermore, the findings from Kazemi et al,corroborate our assertion regarding the anti-inflammatory benefits of probiotics. Their research, too, demonstrated a significant decrease in inflammatory markers following probiotic supplementation. This shared outcome strengthens the generalizability and validity of our findings. [17] Accumulating

evidence points to the potential of probiotics in diminishing inflammatory markers, notably IL-6, in individuals contending with inflammatory bowel disease (IBD). One investigation revealed that a combined treatment involving Pentasa and probiotics led to a notable decline in IL-6 levels among IBD patients. [18] Furthermore, a separate study demonstrated that the probiotic strain Lactobacillus reuteri GroEL could curtail IL-6 production, both in human macrophages and in a murine model of DSS-induced intestinal inflammation. [19] These intriguing findings shed light on the anti-inflammatory properties of probiotics, hinting at their capacity to alleviate inflammation in individuals grappling with IBD.[17-19]

In our study, we explored the impact of specific probiotic strains on gut microbiota composition, with a particular focus on Firmicutes. The findings revealed noteworthy alterations in Firmicutes abundance within the probiotic group. This observation underscores the potential of probiotics to influence the delicate balance of microbial communities in the gut. For instance, a notable study by Ghyselinck et al, explored the impact of Symprove, a multi-strain probiotic, on the gut microbiota of individuals afflicted with ulcerative colitis (UC). Over a mere 48-hour window, this probiotic instigated substantial alterations in bacterial composition. Notably, it bolstered the levels of Firmicutes, a group often found in reduced numbers in UC patients, while simultaneously triggering the production of short-chain fatty acids (SCFAs) and lactate, both celebrated for their salutary contributions to gut health. [20]

In another vein of investigation by Stojanov et al, the interplay between probiotics, the Firmicutes/Bacteroidetes (F/B) ratio, obesity, and IBD was spotlighted. Oral administration of probiotics emerged as a potentially promising avenue for rectifying dysbiosis within the microbiota and averting the onset of obesity or IBD. However, it's vital to underscore that the influence of distinct probiotics on the F/B ratio can diverge, highlighting the importance of judiciously selecting the suitable probiotic species or combinations for achieving the desired effects.[21]

Conclusion

In conclusion, our study underscores the significant potential of probiotic interventions in mitigating clinical scores and inflammatory markers in patients with inflammatory bowel disease. The specific probiotic strains employed exhibited pronounced effects on the gut microbiota composition, particularly with regards to Firmicutes. These findings not only echo the results of prior research but also emphasize the intricate interplay between probiotics, gut microbiota, and the health of individuals with inflammatory bowel disease. While our study contributes to the growing body of evidence supporting probiotics as a valuable adjunct in IBD management, it also highlights the need for further investigation into optimal probiotic strains and their tailored applications. As we navigate the path toward more personalized and efficacious IBD treatments, these insights provide a promising foundation for future research and therapeutic developments.

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