Review Article

A Randomized, Double Blind, Placebo Controlled, Parallel, Multi-Center, Phase 3 Study on Genetic and Clinical Evaluation of Probiotic *Bacillus coagulans* Strain in Patients with Irritable Bowel Syndrome

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Abstract

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder marked by abdominal pain and altered bowel habits, often impairing quality of life. Gut microbiota dysbiosis is increasingly recognized as a contributor to IBS pathogenesis, positioning probiotics as a promising therapeutic approach. This randomized, double-blind, placebo-controlled, multicenter phase III study assessed the efficacy and safety of *Bacillus coagulans* (1×10^9 CFU/day) in adult IBS patients over 90 days. Sixty participants meeting Rome IV criteria were randomized 1:1 to receive probiotic or placebo. Efficacy endpoints included digestive symptom frequency (DSFQ), IBS severity (IBS-SSS), stool consistency (Bristol stool form scale), and health-related quality of life (FDDQL and FBA questionnaires), with safety monitored via laboratory tests and adverse events. Supplementation with *B. coagulans* significantly reduced DSFQ scores by 55.3%, normalized stool consistency in 66.7% of participants, and resolved IBS symptoms in 86.7% as per IBS-SSS. Quality of life improved across domains including activity limitation, anxiety, dietary restrictions, sleep quality, and stress impact, whereas the placebo group showed minimal changes. No serious adverse events occurred, and laboratory parameters remained normal. These results indicate that *Bacillus coagulans* is a safe, well-tolerated, and effective microbiome-targeted intervention for alleviating IBS symptoms and enhancing patient quality of life.

Keywords: Irritable Bowel Syndrome (IBS); Quality of Life; *Bacillus coagulans*

Introduction

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder characterized by recurrent abdominal pain or discomfort accompanied by altered bowel habits, in the absence of identifiable structural or biochemical abnormalities. Clinical manifestations include diarrhea, constipation, or a mixed bowel pattern, often accompanied by bloating, flatulence, and changes in stool consistency [1]. The chronic and relapsing nature of IBS imposes a considerable burden on healthcare systems and significantly reduces patients' quality of life [2]. According to Rome IV criteria, IBS is defined by abdominal pain occurring, on average, at least one day per week over the previous three months,

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associated with defecation and/or changes in stool frequency or form. Based on predominant bowel patterns, IBS is classified as constipation-predominant (IBS-C), diarrhea-predominant (IBS-D), mixed-type (IBS-M), or unclassified (IBS-U). IBS-C is defined by ≥ 25% of stools being hard or lumpy and < 25% loose or watery, whereas IBS-D is characterized by ≥ 25% loose or watery stools and < 25% hard or lumpy. IBS-M involves both stool types ≥ 25% of the time, while IBS-U includes patients whose symptoms do not meet criteria for other subtypes [3].

Globally, IBS affects 15 - 45% of the population, with a higher prevalence in women (female-to-male ratio ~2:1) and symptom onset commonly in early adulthood [4]. The pathophysiology is multifactorial, involving altered gut microbiota composition, small intestinal bacterial overgrowth, dysregulated gastrointestinal motility, visceral hypersensitivity, low-grade mucosal inflammation, and disrupted gut-brain axis signaling [5]. Current therapeutic strategies are largely symptomatic and tailored to subtype and severity, including dietary modifications, pharmacological therapies, and lifestyle or psychological interventions. Dietary approaches, such as low FODMAP diets, may provide symptom relief but are limited by nutritional inadequacy, microbiota disruption, and poor adherence [6,7]. Pharmacological agents, including antibiotics like rifaximin, show variable efficacy and raise concerns about resistance. Lifestyle interventions may provide adjunctive benefits but rarely achieve sustained symptom resolution, highlighting an unmet need for therapies targeting underlying mechanisms rather than symptoms alone [8,9].

Emerging evidence implicates gut microbiota dysbiosis as a central contributor to IBS, positioning microbiome-targeted interventions as promising treatment strategies [10]. Probiotics, defined as live microorganisms conferring health benefits when administered in adequate amounts, have been investigated for their ability to restore gut homeostasis and alleviate IBS symptoms [11]. Among them, *Bacillus coagulans* has attracted attention due to its spore-forming, lactic acid-producing properties, enabling survival in gastric acid and bile [12]. It produces antimicrobial compounds, including coagulin and lactosporin, which inhibit pathogenic bacteria and promote microbial balance. *B. coagulans* also enhances mucosal immune responses and attenuates intestinal inflammation [13]. Clinical studies have shown that supplementation with *B. coagulans* can improve abdominal pain, bloating, diarrhea,

constipation, stool consistency, gastrointestinal motility, and microbial diversity. Importantly, it demonstrates a favorable safety profile without contributing to antibiotic resistance [14,15]. These attributes support *B. coagulans* as a safe and effective microbiome-targeted therapy for IBS management, addressing both symptom relief and underlying pathophysiological mechanisms.

Study Objectives

The primary objective of this study was to evaluate the change in digestive symptom burden from baseline to day 90 using the digestive symptom frequency questionnaire (DSFQ) in patients with irritable bowel syndrome (IBS). Additionally, the study aimed to determine the efficacy of the probiotic *Bacillus coagulans* strain in improving overall gastrointestinal symptoms, IBS severity, and stool consistency. Secondary objectives included assessment of the safety profile of the probiotic intervention and its impact on quality-of-life parameters, laboratory biomarkers, and genetic markers associated with inflammation, metabolism, gut microbiome interactions, and immune response.

Materials and Methods

Study design and ethics

This prospective, randomized, double-blind, parallel-group, placebo-controlled clinical trial was conducted in accordance with the Declaration of Helsinki (2013), ICH-E6(R2) Good Clinical Practice guidelines, New Drugs and Clinical Trials Rules (2019), and ICMR ethical guidelines. Ethical approval was obtained from the Rajalakshmi Hospital Institutional Ethics Committee (Bangalore, India). The trial was prospectively registered with the Clinical Trial Registry of India (CTRI/2024/03/063981).

Participants

Adults aged 18 - 50 years diagnosed with IBS according to Rome IV criteria were enrolled after providing written informed consent. Key exclusion criteria included alarm features, inflammatory bowel disease, celiac disease, immunocompromised status, pregnancy, severe systemic illness, recent antibiotic or probiotic use, or participation in another clinical trial.

Randomization and blinding

Participants were randomized 1:1 using a computer-generated schedule to receive probiotic or placebo. Investigational products

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were identical in appearance and packaging, ensuring blinding of participants, investigators, and study personnel until database lock.

Intervention

The probiotic group received *Bacillus coagulans* (1×10^9 CFU/capsule) orally once daily for 90 days. The placebo group received matching maltodextrin capsules. Concomitant supportive therapy was permitted; antibiotics and other probiotics were prohibited.

Assessments

Study visits included screening, baseline (Day 1), follow-ups (Days 14, 28, 45, 56, and 70), and end-of-treatment (Day 90). Gastrointestinal symptoms were assessed using the digestive symptom frequency questionnaire (DSFQ) and IBS severity scoring system (IBS-SSS). Stool consistency was evaluated using the Bristol stool form scale. Health-related quality of life was assessed using FDDQL and FBA questionnaires. Safety evaluations included physical examination, vital signs, laboratory parameters, and adverse event monitoring.

Outcomes

Primary endpoints were changed from baseline to Day 90 in DSFQ, IBS-SSS, and stool consistency. Secondary endpoints included HRQoL measures, safety outcomes, metabolic parameters, and laboratory biomarkers.

Statistical analysis

Sample size (N = 60) provided 80% power to detect a 20% between-group difference at $\alpha = 0.05$. Analyses were performed using SAS v9.1 on the per-protocol population. Continuous variables were analyzed using paired t-tests and ANOVA; categorical variables were analyzed using chi-square tests. Data are presented as mean ± SD or percentages.

Efficacy evaluation

Irritable bowel syndrome-symptom severity score (IBS-SSS)

The severity of gastrointestinal symptoms in subjects with irritable bowel syndrome (IBS) was assessed using the Rome Foundation-validated IBS symptom severity score (IBS-SSS) questionnaire. The IBS-SSS quantitatively evaluates symptom burden across five domains, including abdominal pain (intensity and frequency), abdominal distension/bloating, dissatisfaction with bowel habits, and the overall impact of IBS on daily life. Each

domain contributes equally to a total score ranging from 0 to 500, with severity categorized as mild (75 - 174), moderate (175 - 299), and severe (300 - 500). Scores below 75 indicate normal bowel function or inactive disease.

At baseline, subjects in the probiotic treatment group demonstrated a broad distribution of IBS severity, with 13 participants classified as mild, 15 as moderate, and 2 as severe. Following treatment with *Bacillus coagulans*, a substantial improvement in symptom severity was observed. By the end of treatment (EOT), the majority of participants reported resolution of symptoms, with 26 subjects achieving IBS-SSS scores indicative of normal bowel function. Only 2 subjects remained in the mild category, while 1 subject each was classified as moderate and severe. The reduction in IBS-SSS severity from baseline to EOT in the probiotic group was statistically significant.

In contrast, the placebo group showed minimal changes in IBS symptom severity over the study period. At baseline, 16 subjects were classified as having mild IBS and 14 as moderate IBS. At EOT, only 1 subject achieved normal bowel function, while 16 and 13 subjects remained in the mild and moderate categories, respectively. No meaningful shift toward symptom resolution was observed, and the change in IBS-SSS scores from baseline to EOT in the placebo group was not statistically significant.

Overall, 86.67% of participants in the probiotic group achieved normal bowel function by the end of treatment, demonstrating a clinically meaningful improvement compared with placebo. These findings indicate that *Bacillus coagulans* supplementation significantly reduced IBS symptom severity, whereas placebo treatment did not result in significant improvement across IBS-SSS severity categories (Figure 1).

Digestive symptoms frequency questionnaire (DSFQ)

Digestive symptom frequency was assessed using the digestive symptoms frequency questionnaire (DSFQ), which evaluates four gastrointestinal symptoms: abdominal pain/discomfort, bloating, flatulence (passage of gas), and borborygmi (rumbling stomach). Individual symptom scores were summed to generate a total DSFQ score ranging from 0 (no symptoms) to 15 (maximum symptom frequency/severity). DSFQ scores were recorded at baseline and throughout the treatment period to assess changes in symptom burden in the probiotic and placebo groups.
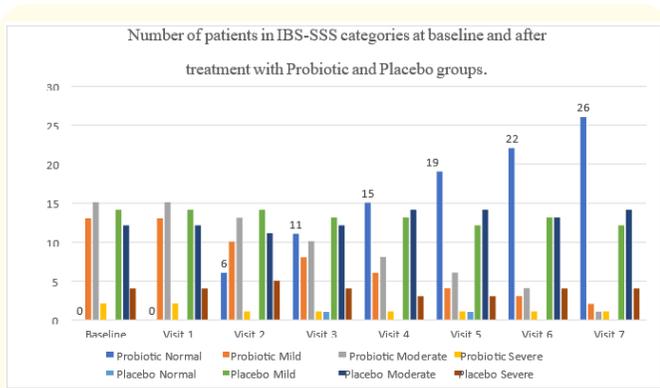
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Figure 1: % Number of patients in IBS-SSS categories at baseline and after treatment with probiotic and placebo groups.

At baseline, mean DSFQ scores were comparable between groups. In the probiotic group, the mean DSFQ score was 10.66 ± 1.11, while the placebo group had a mean score of 11.07 ± 0.63. Over the course of treatment, the probiotic group demonstrated a consistent and progressive reduction in DSFQ scores across visits. By the end of treatment (EOT; Visit 7), the mean DSFQ score in the probiotic group decreased significantly to 4.76 ± 1.12, corresponding to a 55.34% reduction from baseline.

In contrast, the placebo group did not exhibit sustained improvement in digestive symptoms. Mean DSFQ scores increased slightly from 11.07 ± 0.63 at baseline to 12.27 ± 1.36 at EOT, representing a 10.83% increase in symptom frequency over the study period (Figure 2).
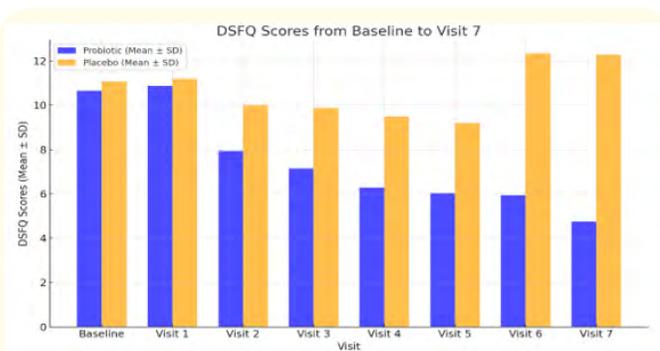

Figure 2: Digestive symptoms frequency questionnaire (DSFQ) scores from baseline to visit 7 after treatment with probiotic and placebo groups.

Analysis of percentage change from baseline further illustrated the divergence between treatment groups. In the probiotic group, DSFQ scores showed a progressive and sustained reduction beginning at visit 2 (-25.61%), which continued through subsequent visits, reaching -55.35% by visit 7. This pattern reflects a continuous improvement in digestive symptom frequency over time. In contrast, the placebo group demonstrated only modest and inconsistent changes, with small reductions observed up to Visit 5 (maximum -16.89%), followed by a rebound increase in symptom scores at visits 6 and 7, resulting in an overall worsening relative to baseline.

Collectively, these findings demonstrate that probiotic supplementation resulted in a clinically meaningful and sustained reduction in digestive symptom frequency, whereas placebo treatment was associated with minimal and inconsistent changes. The DSFQ results, as depicted in figure 3, highlight the superior efficacy of the probiotic intervention in alleviating digestive symptoms compared with placebo.
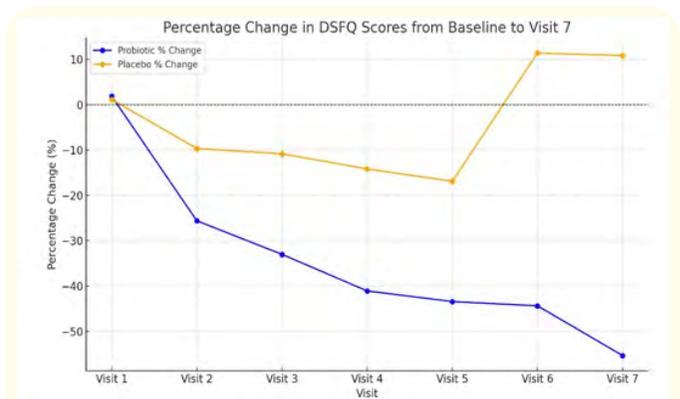

Figure 3: DSFQ scores from baseline to visit 7 after treatment with probiotic and placebo groups.

Stool consistency assessment (Bristol stool form scale)

Stool form was evaluated using the Bristol stool form scale (BSFS; types 1-7, with type 4 considered normal). At baseline, both groups had comparable distributions, with most participants reporting hard stools (Probiotic: Type 1, 36.7%; type 2, 40.0%; type 4, 3.3%; Placebo: Type 1, 33.3%; type 2, 33.3%; type 4, 3.3%).

By visit 7, 66.7% of participants in the probiotic group achieved normal stool consistency (Type 4), while hard stools (Types 1-2)

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decreased to 3.3% each. In contrast, the placebo group showed minimal change, with only 6.7% achieving type 4 and 56.7% remaining in types 1-2. These findings indicate that probiotic supplementation effectively normalized stool consistency, whereas placebo had limited impact.

Figure 4: Stool consistency assessment (Bristol stool from scale) in probiotic and placebo groups.

Assessment of health-related quality of life (HRQoL) using FDDQL

HRQoL was assessed using the FDDQL questionnaire (eight domains; scores 0-100, higher scores indicate greater impairment). At baseline, both groups exhibited severe impairment across all domains (mean ≥ 78) with comparable scores.

By end of treatment (Visit 7), the probiotic group showed marked improvements across all domains, with scores shifting to minimal or mild impact: activity limitation (84.7 → 22.3), anxiety (86.2 → 24.8), dietary restrictions (85.6 → 22.3), sleep (89.5 → 28.6), discomfort (78.6 → 26.4), negative health perception (85.5 → 23.7), coping (79.7 → 25.7), stress impact (83.2 → 26.5), and global symptom severity (84.6 → 18.5). In contrast, the placebo group showed minimal change, with most domains remaining in the severe impact range and global symptom severity decreasing only slightly (85.6 → 82.4).

These results demonstrate that probiotic supplementation significantly and clinically improved HRQoL, encompassing daily functioning, psychological well-being, symptom burden, and stress, whereas placebo had limited effect.
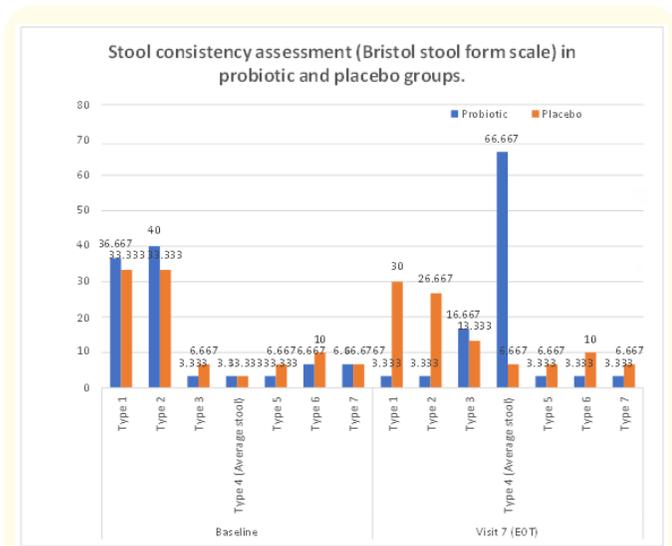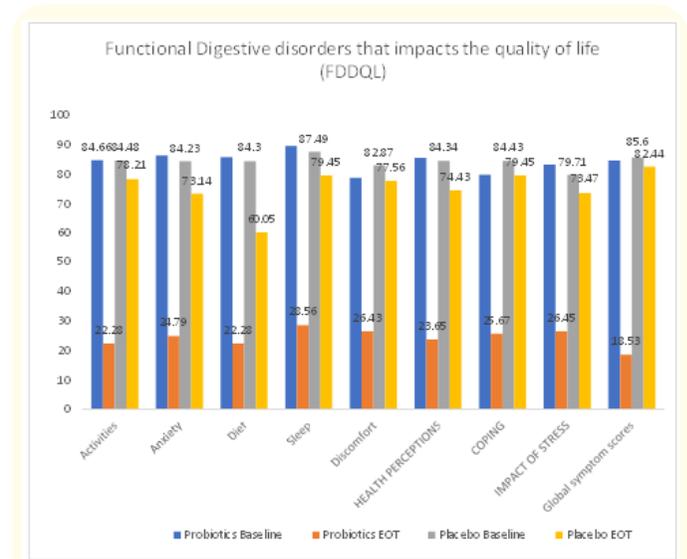

Figure 5: Functional digestive disorders quality of life (FDDQL) questionnaire scores assessment between probiotic and placebo groups that impacts quality of life.

Food-based assessment (FBA) QOL questionnaire

The FBA quality of life (QOL) assessment evaluated the impact of various domains on quality of life in individuals across two groups: Probiotic and placebo. The assessed QOL domains included reduced physical symptoms and discomfort, improved dietary adaptability, improved social and emotional well-being, better work and activity performance, improved sleep quality, enhanced physical health, reduced mental health distress, high treatment satisfaction, and improved overall quality of life. At baseline, both groups demonstrated high QOL impairment scores, indicating significant impacts from functional bowel ailments. However, the probiotic group exhibited significant reductions in QOL impairment scores across all domains by the end of treatment (EOT), with notable improvements in treatment satisfaction and overall quality of life, compared to the placebo group, which showed minimal changes.
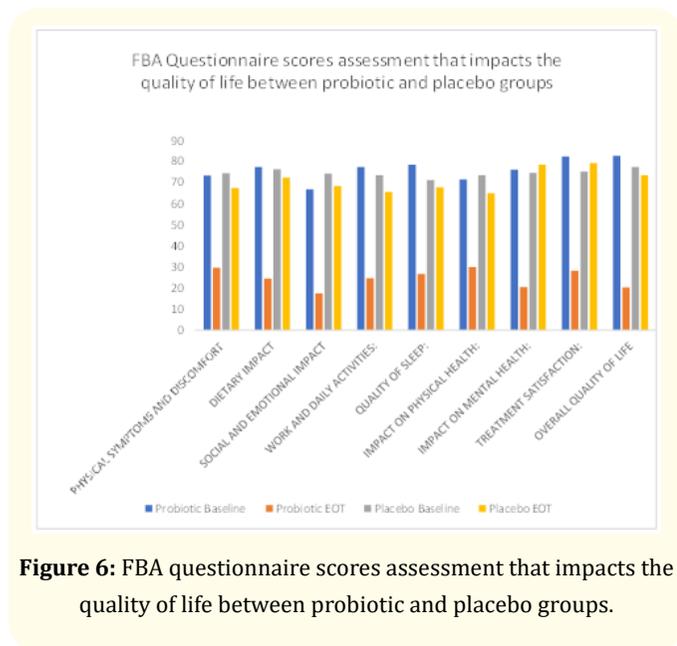
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Figure 6: FBA questionnaire scores assessment that impacts the quality of life between probiotic and placebo groups.

Discussion and Conclusion

This randomized, double-blind, placebo-controlled, multicenter phase III study demonstrates that *Bacillus coagulans* is a safe, well-tolerated, and effective therapeutic option for patients with IBS. Probiotic supplementation produced clinically meaningful and sustained improvements in digestive symptoms, stool consistency, and health-related quality of life compared with placebo.

Treatment with *B. coagulans* resulted in a significant 55.3% reduction in digestive symptom frequency (DSFQ), with improvements evident early and maintained throughout the 90-day intervention. In contrast, placebo recipients showed no meaningful symptom improvement. Marked benefits were also observed in HRQoL, with substantial reductions across all FDDQL domains, including activity limitation, anxiety, dietary restrictions, sleep disturbance, discomfort, coping ability, and stress impact. Global symptom severity improved dramatically in the probiotic group, shifting from severe impairment at baseline to minimal impact at study completion, while placebo-treated subjects exhibited minimal change.

Stool consistency normalized in 66.7% of probiotic-treated participants compared with only 6.7% in the placebo group, indicating effective modulation of bowel function. Importantly, no serious adverse events were reported, and laboratory parameters remained within normal ranges, confirming the favorable safety profile of *B. coagulans*.

Overall, once-daily supplementation with *Bacillus coagulans* (1×10^9 CFU) over 90 days significantly improved gastrointestinal symptoms, bowel habits, and quality of life in IBS patients. These findings support *B. coagulans* as an effective microbiome-targeted therapeutic intervention for the management of IBS and other functional bowel disorders.

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