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Research Article

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

Prabhu Rajagopalan[1], Raksha Sunhare[1], Shyamprasad Kodimule[1] and Subhendu Nayak[2]*

[1]Development and Research Centre-Probiotics, Vidya Herbs Pvt Ltd, No. 102B and 105B, Pharmaceuticals SEZ Industrial area, KIDB, Hassan, 573201 Karnataka, India

[2]Vidya USA Corporation, 7 Otis Stone Hunter Road, Bunnell, FL 32100, USA

***Corresponding Author:** Subhendu Nayak, Vidya USA Corporation, 7 Otis Stone Hunter Road, Bunnell, FL 32100, USA.

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Abstract

Objective: This study evaluated the efficacy and safety of oral *A. muciniphila* supplementation (Test Product) compared to *Bifidobacterium lactis* and *Lactobacillus plantarum* (Control Product) and placebo in individuals with irritable bowel syndrome. The primary objective was to assess improvements in digestive symptoms; the secondary objective was to evaluate safety and tolerability.

Methods: In this multicentred, randomized controlled trial, adults (18–50 years) with irritable bowel syndrome (Rome IV criteria) received a daily test product, a control product, or a placebo for 12 weeks. Primary outcomes included changes in irritable bowel syndrome Symptom Severity Score. Secondary measures included quality of life, metabolic and liver parameters, stool characteristics, and safety assessments. Intention-to-treat analyses were performed.

Results: *Akkermansia muciniphila* supplementation resulted in a 47% reduction in DSFQs and a significant decrease in IBS-SSS (143 to 27; p = 0.034). Notable metabolic improvements (reductions in cholesterol, triglycerides, liver enzymes) were observed with *Akkermansia muciniphila*. No significant adverse events were reported; safety and tolerability were confirmed.

Conclusion: These findings indicate *Akkermansia muciniphila* potential as an irritable bowel syndrome treatment and emphasise the need for larger, long-term trials to prove its mechanistic and clinical effects.

Keywords: *Akkermansia muciniphila*; *Bifidobacterium lactis*; Irritable Bowel Syndrome; *Lactobacillus plantarum,* Next-Generation Probiotics

Introduction

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder globally, affecting approximately 10% to 15% of the population, making it one of the most frequently encountered functional gastrointestinal disorders in clinical practice [1]. The etiology of IBS is multifactorial and not yet fully understood. It is believed to arise from a combination of factors, including abnormal gastrointestinal motility, visceral hypersensitivity,

gut-brain axis dysregulation, and alterations in gut microbiota composition [2]. Physiological and psychological factors, such as diet modulation, exercise, sleep disturbance, stress, anxiety, and depression, also play a significant role in the exacerbation of IBS symptoms, contributing to its classification as a disorder of the gut-brain interaction [3]. Research indicates that individuals with IBS may exhibit an imbalance in gut microbial communities, which has been linked to increased gut permeability and inflammation [4].

Probiotics are proven for their potential adjunct therapy for IBS, as they may help restore gut microbiota balance and improve gastrointestinal function [5]. These beneficial bacteria primarily belong to the genera *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, and, more recently recognized, *Akkermansia*. Numerous clinical studies have explored the efficacy of various probiotic strains in alleviating IBS symptoms [6,7]. Meta-analyses have demonstrated that probiotics can significantly reduce the severity of abdominal pain and bloating, improve overall gut health, and enhance quality of life for individuals with IBS [8]. The effectiveness of probiotics may vary based on the specific strains used, dosage, treatment duration, and individual patient characteristics. For instance, *Lacto-bacillus* and *Bifidobacterium* species have been shown to be particularly effective in reducing IBS symptoms [9]. The mechanisms by which probiotics exert their beneficial effects include the modulation of gut microbiota, enhancement of the intestinal barrier function, competition with pathogens for adhesion sites, and the production of antimicrobial substances, such as short-chain fatty acids and bacteriocins [10].

Among these, *Akkermansia muciniphila* has gained attention for its potential therapeutic benefits in IBS due to its role in gut barrier function and immune modulation [7]. Derrien., *et al*. (2019) provides a comprehensive review on the development and evolution of the gut microbiota during the first decade of life, emphasizing its dynamic nature from birth through childhood [11]. Cani., *et al*. (2008) demonstrated that changes in gut microbiota can control metabolic endotoxemia-induced inflammation and thereby impact obesity and diabetes in mice [3]. Specifically, mice fed a high-fat diet had a marked reduction (by a factor of 100) in certain beneficial gut bacteria, particularly *Akkermansia muciniphila*, compared to those on a standard diet [12].

Akkermansia muciniphila is a mucin-degrading bacterium that is gaining attention for its potential role in human health and metabolic disorders. Discovered in 2004, this Gram-negative, anaerobic bacterium (about 3–5% of adult gut microbiota) is a member of the phylum Verrucomicrobia and is predominantly found in the human gastrointestinal tract, particularly in the mucus layer of the intestine [13]. The unique ability of *A. muciniphila* to utilize mucin as its primary energy source allows it to thrive in the mucus layer that lines the intestinal epithelium. By degrading mucin, *Akkermansia muciniphila* contributes to the turnover of the mucus layer, which is essential for gut barrier function and integrity. The degradation process results in the production of short-chain fatty acids (SCFAs) and other metabolites, which can enhance the health of the intestinal epithelium and modulate immune responses [10]. Recent studies have shown promising results, with *Akkermansia muciniphila* supplementation leading to significant improvements in IBS symptoms, including reduced abdominal pain, bloating, and overall gastrointestinal discomfort.

The present clinical study is a randomized, double-blind, placebo-controlled, parallel, multicenter, phase 3 trial designed to evaluate the genetic and clinical efficacy of the probiotic *Akkermansia muciniphila* in patients diagnosed with IBS. This study evaluates the efficacy and safety of *Akkermansia muciniphila* (Test Product group) compared to *Bifidobacterium lactis* and *Lactobacillus Plantarum* (Control Product group) and a Placebo in managing irritable bowel syndrome. By utilizing a robust study design, this trial aims to provide comprehensive insights into the safety and efficacy of this probiotic strain, addressing an urgent need for effective treatment options in IBS management. This study will not only evaluate clinical outcomes but also explore the genetic underpinnings of the response to *Akkermansia muciniphila*, thereby contributing to the understanding of personalized medicine approaches in the management of IBS.

Methods and Materials

This multicentric study enrolled adult patients meeting Rome IV criteria [2] for IBS [14]. Participants were randomized to receive either a daily oral dose of *Akkermansia muciniphila*, or *Bifidobacterium lactis* and *Lactobacillus Plantarum* combination, or a placebo for 12 weeks.

Study selection

- **Inclusion Criteria**: 1) Age 18 Years to 50 Years. 2) Both males and females. 3) Patients should fulfil Rome Foundation IBS-Diagnostic Questionnaire. 4)Patients are willing to

provide written informed consent and comply with protocol requirements.

- **Exclusion Criteria:** 1) Any patient with weight or appetite loss, iron deficiency anaemia, fever or rectal bleeding. 2) Known inflammatory bowel disease or celiac disease patients. 3) Immuno-compromised patients. 4) Pregnancy or wishing to become pregnant during study. 5) End-stage kidney failure on dialysis, presence of other diseases, including cancer or severe. 6) Hepatic insufficiency (transaminases >3.5x above normal). 7) The use of other probiotic products or antibiotics over the previous 6 months. 8) Participation in other clinical trials.

Treatments administered

- Test Product- 5.0 billion CFU/capsule of *Akkermansia muciniphila* VHAKM6l4 of Batch Number: VP5/F/23/11/001 Mfg. date: Nov. 2023, Exp. Date: Dec 2025
- Control Product- 2.0 billion CFU/capsule of *Bifidobacterium lactis* VHBBL 36 (Batch Number: VP12/F /23/11/006) *and* 3.0 billion CFU/capsule *Lactobacillus plantarum* VHLP-39 (VP4/ F/23/09/0013) of Nov. 2023, Exp. Date: Dec 2025
- Placebo: Non-GMO Corn Maltodextrin, Batch Number: F-34210/22-08

Data extraction

A day of treatment, screening, and enrolment of the patient based on the informed consent, Demographic data, medical and surgical history, medication history, and physical examination.

Till the 7 weeks (90 days) for outcome measure and quality assessments. 1) Physical examination. 2) Vital signs. 3) Concomitant medications. 4) Adverse events (if any). 5) Subject's assessment of tolerability of treatment. 6) Collection of patient diary and checking treatment compliance. 7) Collection of remaining study medication. 8) Reassessment of genetic markers related to protein metabolism, inflammation, gut microbiome interactions, and immune response. 9) Final measurements of gastrointestinal symptoms, IBS severity (IBS-SSS), and stool consistency (Bristol stool form scale). 10) Assessments of HRQoL, FBA, and FDDQL. 11) Analysis of hematological and hepatic biomarkers, fasting blood sugar level, HbA1c, and lipid profile parameters. 12) Vital signs and physical examination. 13) Reporting of all adverse events throughout the study duration.

Quality assessment and statistical analysis

The primary outcome was the improvement in IBS symptom severity, measured using the IBS Severity Scoring System (IBS-SSS). Secondary outcomes included safety, tolerability, quality of life (IBS-QoL), stool frequency and consistency (Bristol Stool Form Scale). Digestive Symptom Frequency Questionnaire (DSFQ), Changes in HRQoL (FBA and FDDQL) from Visit 1 to Visit 7. Changes in Haematological and hepatic biomarkers, fasting blood sugar level, HbA1c, and lipid profile parameters. Changes in genetic markers associated with protein metabolism, inflammation, gut microbiome interactions, and immune response. Data was analyzed using intention-to-treat principles.

Results

Irritable bowel syndrome-stool severity score

The Irritable Bowel Syndrome Symptom Severity Score (IBS-SSS) is a valuable tool for assessing symptom severity in IBS patients. It quantifies IBS's impact on daily life and helps both healthcare providers and patients monitor improvement. The IBS-SSS questionnaire evaluates five key areas with a total possible score ranging from 0 to 500.

- **Pain Severity:** Rates the severity of abdominal pain on a scale from 0 (no pain) to 100 (extremely severe pain).
- **Pain Frequency:** Measures of how often the pain occurs, rated from 0 (never) to 100 (always).
- **Bloating**: Rates the experience of bloating from 0 (no bloating) to 100 (extremely severe bloating).
- **Bowel Dysfunction:** Includes aspects such as frequency of bowel movements and urgency, rated from 0 (no issues) to 100 (severe dysfunction).
- **Quality of Life:** Rates how much IBS impacts daily life and overall well-being, from 0 (no impact) to 100 (extremely severe impact).

Patients' individual scores were averaged in the Test Product, Control Product, and Placebo. These were then compared at baseline and visit 7 (Figure 1). The Test Product was found to have a significant reduction in IBS-SSS avg. score from the baseline to visit 7, reducing from 143 to 27 (p value = 0.034). The Control Product showed no significant reduction in the IBS-SSS avg. score

reduced from 136 to 94. (p value = 0.532). Placebo showed no significant change in the IBS-SSS score and the avg. score enhanced from 139 to 150. Additionally, the changes in symptom severity for IBS patients across three study groups—Test Product, Control Product, and Placebo—at baseline and after treatment (Visit 7) are represent in Table 1.

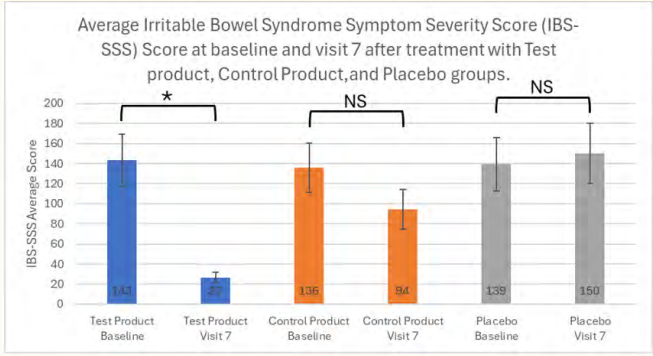


Figure 1: Average Irritable Bowel Syndrome Symptom Severity Score (IBS-SSS) Score at baseline and visit 7 after treatment with Test Product, Control Product, and Placebo groups.

Variable	Test Product (N = 30) %		Control Product (N = 30) %		Placebo (N = 30)	
	Baseline	Visit 7	Baseline	Visit 7	Baseline	Visit 7
Minimal symptoms (<75)	3.33	83.33	3.33	40	3.33	3.33
Mild (75- 175)	46.67	6.67	50	23.33	46.67	40
Moderate (175-300)	33.33	6.67	33.33	26.67	36.67	40
Severe (>300)	16.67	3.33	13.33	10	13.33	16.6

Table 1: Percentage of Patients with IBS-SSS at Baseline vs. Visit 7 (Post-Treatment).

Data represented as mean SD. *P < 0.0001.

- **Minimal/No Symptoms (0-74)**: Only 1 patient in each group (Test Product, Control Product, Placebo) experienced little or no symptoms at baseline. By Visit 7, 25 Test Product patients had decreased or no symptoms. Twelve Control Product patients met this criteria. However, the placebo group remained at 1 patient with minimal symptoms.
- **Mild Symptoms (75-174)**: At the start of the trial, 14 Test Product, 15 Control Product, and 14 Placebo individuals experienced minor symptoms. By Visit 7, the Test Product group had 2 mildly symptomatic patients and the Control Product group had 7. The placebo group improved little, with 12 patients at mild symptoms.
- **Moderate Symptoms (175-299)**: Initially, 10 Test Product, 10 Control Product, and 11 Placebo patients experienced moderate symptoms. Moderate symptoms decreased to 2 in the Test Product group and 8 in the Control Product group by Visit 7. The placebo group showed no improvement, with 12 patients still having moderate symptoms.
- **Severe Symptoms (300-500)**: At baseline, 5 Test Product, 4 Control Product, and 4 Placebo patients reported severe symptoms. By Visit 7, only 1 patient in both testing product groups and 3 in control product groups were severe, indicating symptom relief. Five placebo patients persisted with significant symptoms.

Test Product groups reduced symptom severity across all categories, with many patients improving to minimal or no symptoms. The Test Product reduced service symptoms across all categories better than the Test Product and Control Product. The placebo group had no improvement, with symptoms remaining the same throughout the research.

Digestive symptoms frequency questionnaire (DSFQ)

The frequency of 4 digestive symptoms (abdominal pain/discomfort, bloating, flatulence/passage of gas, and borborygmi/rumbling stomach) was evaluated using the DSFQ. The Digestive Symptoms Frequency Questionnaire (DSFQ) was employed to quantify gastrointestinal symptom burden (Figure 2). Abdominal pain frequency over the past 3 months was scored as: not relevant = 0, 1 day/week = 1, 2 days/week = 2, and 3 days/week = 3. Bloating, flatulence, and borborygmi were each scored as: not relevant = 0, not at all = 1, a little = 2, a lot = 3, and very much = 4. Individual scores were summed to yield a total DSFQ score ranging from 0 (no reported symptoms) to 15 (greatest symptom frequency/severity).

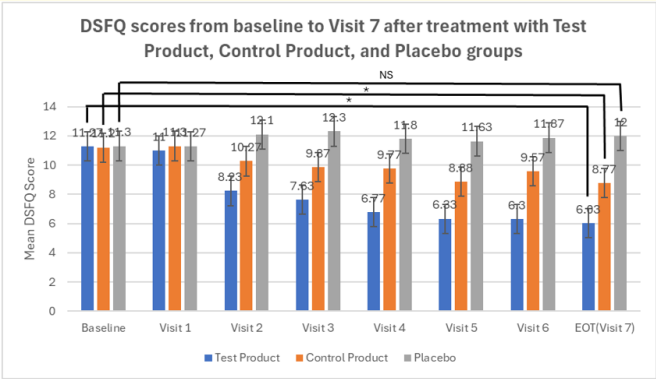


Figure 2: DSFQ means scores from baseline to Visit 7 after treatment with Test Product, Control Product and Placebo groups.

The results of the study clearly demonstrate the efficacy of both the probiotic and Control Product interventions in improving digestive symptoms, as reflected by significant reductions in DSFQ scores over time. The Test Product group consistently outperformed the Control Product group, particularly by the end of the study (Visit 7), achieving a 47% reduction compared to a 22% reduction in the Control Product group.

In contrast, the Placebo group showed no meaningful improvement, with scores remaining nearly unchanged from baseline (12.00 ± 1.06 at Visit 7 vs. 11.30 ± 1.24 at Baseline). These findings underscore the potential benefit of Probiotic intervention as a more effective treatment option for managing digestive symptoms compared to the Control Product and Placebo groups.

Stool consistency assessment (Bristol Stool Form Scale)

The Bristol stool scale is a diagnostic medical tool designed to classify the form of human feces into seven categories. The seven types of stools are: Type 1: Separate hard lumps, like nuts (difficult to pass); Type 2: Sausage-shaped, but lumpy; Type 3: Like a sausage but with cracks on its surface; Type 4: Like a sausage or snake, smooth and soft (average stool); Type 5: Soft blobs with clear cut edges; Type 6: Fluffy pieces with ragged edges, a mushy stool (diarrhea); Type 7: Watery, no solid pieces, entirely liquid (diarrhea).

At Visit 7, the Test Product Group had a significant shift towards normal stool consistency (Type 4) when examining the seven stool types in the Bristol Stool Form. At Visit 7, there was a significant shift towards normal stool consistency (Type 4) in the Test Product and Control Product groups, while the Placebo group showed little or no improvement. The data indicates a positive change in stool consistency for the Test Product and Control Product groups compared to the Placebo group (Figure 3).

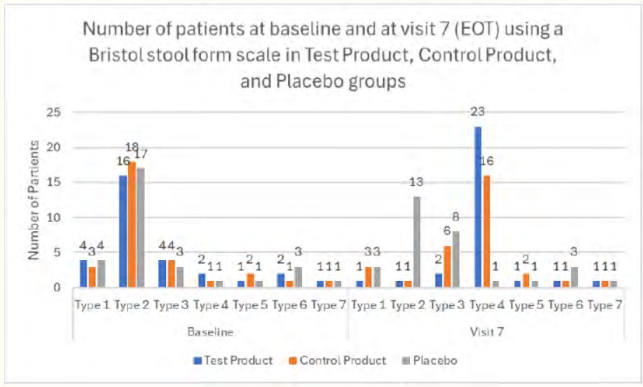


Figure 3: Number of patients at baseline and at visit 7 (EOT) using a Bristol stool form scale in Test Product, Control Product and placebo groups.

Assessments of HRQOL (FBA AND FDDQOL)

The complete, validated Functional Digestive Disorders Quality of Life (FDDQL) questionnaire assesses how digestive disorders affect health-related quality of life. Based on symptom intensity and daily life effect, the FDDQL provides valuable insights into patients' lives. Domain scores are 0–100, where:

- 0 signifies minimal impact (e.g., no limitations or symptoms), and
- 100 indicates the most severe impact (e.g., extreme limitations or debilitating symptoms).

The questionnaire encompasses 43 items organized into 8 key domains that reflect different facets of HRQOL:

- **Daily Activities:** Evaluates the extent to which digestive issues interfere with routine tasks (8 items).
- **Anxiety:** Assesses the psychological toll of digestive health concerns (5 items).
- **Dietary Restrictions:** Measures the limitations imposed on eating habits due to digestive disorders (6 items).
- **Sleep:** Captures disruptions to sleep quality and duration caused by symptoms (3 items).
- **Discomfort:** Focuses on the intensity and frequency of physical discomfort (9 items).
- **Coping:** Explores the individual's ability to adapt to and manage their condition (6 items).
- **Disease Control:** Reflects the perceived control over symptoms and their impact (3 items).
- **Impact of Stress:** Highlights the role of stress in exacerbating digestive symptoms (3 items).

This study used the FDDQL questionnaire at baseline (pre-treatment) and Visit 7 (end-of-treatment) to measure symptom progression and intervention efficacy. Individually, participants answered the questionnaire using 5- or 6-point Likert scales for each issue. The domain-specific and total scores provided a detailed view of HRQOL changes during treatment. Table 2 shows how probiotics and placebo affected functional digestive disorder patients' FDDQL questionnaire quality of life. Domain-specific scores are gathered at baseline and end-of-treatment.

QOL Domain	Test Product (N = 30)		Control Product (N = 30)		Placebo (N = 30)	
	Baseline	Visit 7	Baseline	Visit 7	Baseline	Visit 7
Activity Limitations	64.76 ± 4.02	32.14 ± 3.58	64.13 ± 4	42.87 ± 1.62	65.48 ± 3.74	64.21 ± 1.46
P value	0.006		0.009		0.152	
High Anxiety Levels	65.77 ± 8.29	33.59 ± 3.02	64.62 ± 9.17	47.89 ± 3.09	67.05 ± 7.47	63.97 ± 3.84
P value	0.007		0.009		0.183	
Dietary Restrictions	63.54 ± 7.36	37.29 ± 3.66	61.25 ± 6.85	55.3 ± 3.09	62.4 ± 5.71	61.04 ± 3.36
P value	0.006		0.07		0.161	
Disturbed Sleep	70.22 ± 8.71	31.56 ± 6.05	68 ± 10.71	48.67 ± 5.3	70 ± 8.71	70.89 ± 6.19
P value	0.008		0.013		0.223	
Discomfort	64.4 ± 7.09	28.44 ± 2.76	63.12 ± 7.29	44.52 ± 2.71	63.76 ± 5.87	58.23 ± 3.18
P value	0.005		0.011		0.287	
Negative Health Perceptions	67.33 ± 5.9	43.79 ± 18.14	66.67 ± 4.29	47.58 ± 17.86	66.22 ± 5.52	60.33 ± 17.72
P value	0.018		0.022		0.175	
Poor Coping Ability	65.78 ± 3.71	36.44 ± 4.54	65.78 ± 2.89	43.11 ± 5.05	66.89 ± 6.19	68.89 ± 5.89
P value	0.009		0.017		0.188	
High Impact of Stress	63.11 ± 6.19	36.22 ± 6.48	62.89 ± 3.36	40.22 ± 8.53	67.56 ± 5.46	70.67 ± 4.14
P value	0.007		0.015		0.198	
Global Symptom Severity	61.25 ± 5.23	34.49 ± 3.03	58.78 ± 4.69	49.51 ± 2.46	65.5 ± 4.06	60.74 ± 2.57
P value	0.006		0.028		0.273	
P value: Baseline vs EOT ; Data represented as mean SD. *P < 0.0001.						

Table 2: FDDQL Score Assessment: Test vs. Control vs. Placebo.

The Test Product group improved in all quality-of-life dimensions, including activity constraints, anxiety, dietary restrictions, disturbed sleep, discomfort, health perceptions, coping abilities, stress, and global symptom intensity. The Test Product group achieved the greatest improvements in Activity Limitations, Coping Ability, and Global Symptom Severity, surpassing the Control Product group. Though less noticeable than the Test Product group, the Control Product group improved across all domains. The placebo group showed little to no improvement and sometimes worsened symptoms including sleep quality and stress. These findings show that Test Product treatments improve quality of life for functional digestive problem patients better than Placebo.

Functional bowel disorders quality of life (FBA) QOL questionnaire

In the FBA Quality of Life (QOL) Assessment, test, control, and placebo groups were assessed for quality of life. Reducing Physical Symptoms and Discomfort, Dietary Adaptability, Social and Emotional Well-being, Work and Activity Performance, Sleep Quality, Physical Health, Mental Health Distress, High Treatment Satisfaction, and Overall Quality of Life were assessed QOL domains (Figure 4). Both groups had high baseline QOL impairment scores, demonstrating functional bowel disease's impact. By the end of treatment (EOT), the Test Product group had significantly lower QOL impairment scores across all domains, better treatment satisfaction, and overall quality of life than the Control Product and Placebo groups. All quality-of-life areas, including physical symptoms, dietary adaptation, social and emotional well-being, activity performance, sleep quality, physical health, and mental health, improved significantly for the Test Product group. Also, treatment satisfaction and quality of life improved dramatically. The Test Product group improved sleep quality, physical health, and mental health distress consistently. The Control Product group showed favourable effects across all areas, albeit not as strongly as the Test Product. The placebo group exhibited little to no improvement, including mental health concerns. These data show that the Test Product interventions improve quality of life better than the Placebo and Control Product groups, making them a good option for functional disorder patients.

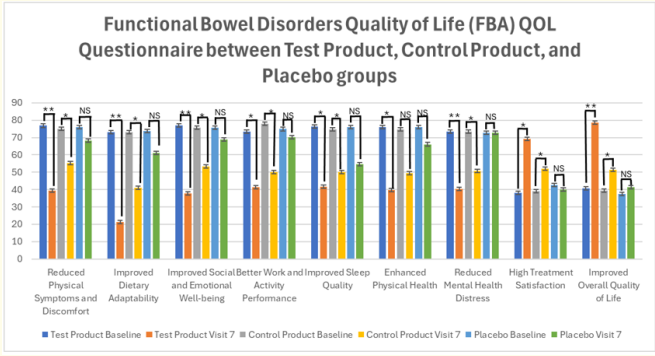


Figure 4: Functional Digestive Disorders Quality of Life (FDDQL) Questionnaire scores assessment between Test Product, Control Product and placebo groups.

5B CFU Akkermansia supplementation improves digestive gene expression

Participants were randomised to the Test Product (probiotics), Control Product (control), and Placebo groups. IL-6, TNF alpha, FUT-2, and GCKR were assessed at screening and EOT. Data has been categorised as Up-Regulated (increased IL-6, TNF alpha, FUT-2, and GCKR), Down-Regulated, or No Change. RT-PCR was employed to measure serum IL-6, TNF alpha, FUT-2, and GCKR levels, normalising relative expression to housekeeping genes and estimating concentrations using standard curves. Paired t-tests assessed within-group changes, and comparison analysis compared Probiotic and Placebo groups (Tables 3). IL-6, TNF-alpha, and FUT-2 in the Test Product Group changed significantly towards the end of the trial, indicating molecular digestion improvements.

Immunoglobulin levels (IgA, IgM, IgG)

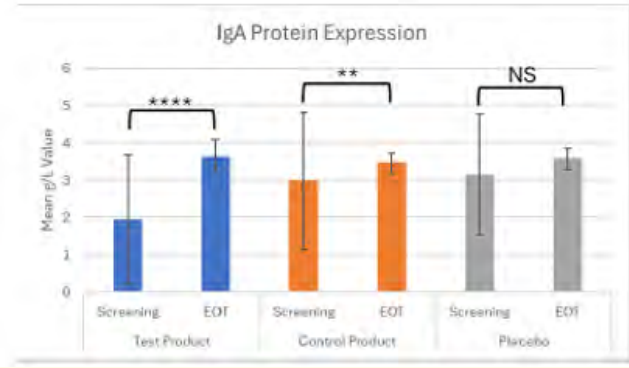
IBS patients are tested for immunological modulation by the probiotic Akkermansia muciniphila. IgA, IgM, and IgG levels were compared between probiotic and placebo groups. Serum samples at screening and end-of-treatment were used to measure immunoglobulin levels by ELISA (Figure 5). The results suggest that probiotics may help treat IBS by regulating mucosal and systemic immunity. Test Product Group: Stronger immunomodulatory effects across all criteria, showing immunological enhancement superiority. Control Product Group: The data imply Control Product supports systemic immunity, notably IgM elevation and mucosal

IL-6					
Group	**Screening**	**End of Treatment**	**ETO-Screening**	**Gene Expression Interpretation**	**P-Value**
Test Product	23.575	28.859	5.284	Down Regulated	0.0001
Control Product	23.649	25.88	2.231	Down Regulated	0.043
Placebo Group	22.55	23.02	0.47	No Change	0.125
TNF Alpha					
Group	Screening	End of Treatment	ETO-Screening	Gene Expression Interpretation	P-Value
Test Product	30.312	35.06	4.748	Down Regulated	0.043
Control Product	31.741	33.88	2.139	Down Regulated	0.049
Placebo Group	31.418	31.963	0.545	No Change	0.552
FUT-2					
Group	Screening	End of Treatment	ETO-Screening	Gene Expression Interpretation	P-Value
Test Product	25.999	22.925	-3.074	Up Regulated	0.046
Control Product	25.391	23.46	-1.931	No Change	0.223
Placebo Group	23.493	23.829	0.335	No Change	0.866
GCKR					
Group	Screening	End of Treatment	ETO-Screening	Gene Expression Interpretation	P-Value
Test Product	27.025	26.01	-1.015	No Change	0.257
Control Product	27.285	28.242	0.957	No Change	0.4
Placebo Group	26.451	27.496	1.046	No Change	0.494

Table 3: Genetic expression analysis of the Test, Control and Placebo**.**

Data represented as mean SD. *P < 0.0001.

immunity (IgA). A placebo group showed no significant changes in IgM, IgA, or IgG. Test and Control Products have immunomodulatory potential, as shown by these observations.



5B CFU *Akkermansia* supplementation improves digestive enzyme expression

ELISA testing on patient serum examined intestinal genetic marker alterations. From screening to study end, enzyme concentration was utilised to express genetic mark changes. This study examines how probiotics affect serum amylase levels in IBS patients. Amylase levels were compared between probiotic

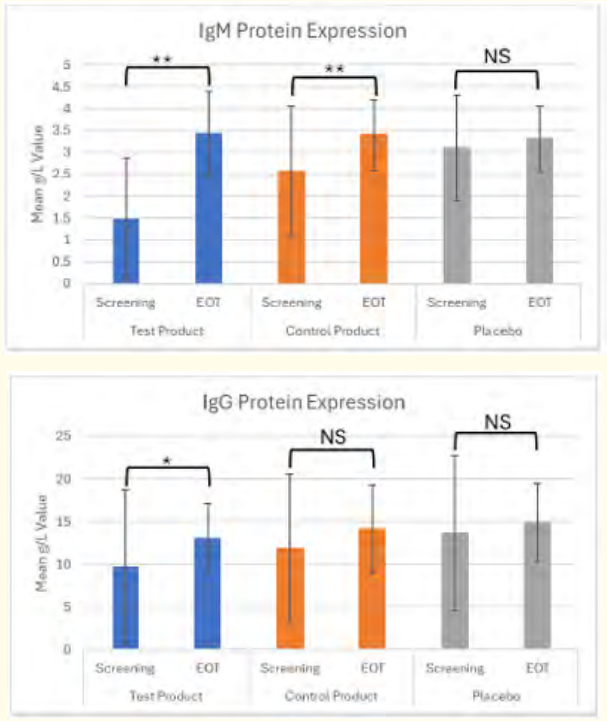


Figure 5: Protein expression of diffèrent markers for the Test Product, Control Product and Placebo group observed through ELISA test.

and placebo groups. Screening and end-of-treatment serum samples were used to quantify amylase levels using conventional biochemical tests. The findings suggest that probiotics may modulate digestive enzyme function, suggesting adjuvant IBS treatments (Table 4).

Test product

- A statistically significant mean increase of 9.792 U/L in serum amylase levels was observed ($p < 0.000240$).
- This suggests that the probiotic intervention had a measurable and positive impact on serum amylase activity, enhancing digestive enzyme function in patients.

Control product group

- A moderate but not statistically significant increase of 5.924 U/L in serum amylase levels was noted ($p = 0.201$).
- This suggests that the Control Product treatment had a mild but not significant effect on serum amylase activity.

Placebo group

- A 0.761 U/L no change mean in serum amylase levels was noted ($p = 0.507$).
- This indicates no observed change in the Placebo group.

The Test Product Group showed the greatest improvement in serum amylase activity compared to the Control Product Group and the Placebo Group, confirming the idea that probiotics may improve digestive enzyme performance. Probiotics may help treat IBS, according to these studies. More research is needed to confirm these findings and understand mechanisms.

Discussion

This randomized, placebo-controlled clinical study investigated the efficacy, safety, and quality-of-life impact of the novel probiotic strain *Akkermansia muciniphila* in comparison to a combination of *Bifidobacterium lactis* and *Lactobacillus plantarum* and a placebo in patients with irritable bowel syndrome (IBS). A total of 90 patients were enrolled and assessed for changes in IBS Symptom Severity Score (IBS-SSS), quality of life (QOL) domains, and safety/tolerability parameters over the intervention period.

Efficacy outcomes

- *Akkermansia muciniphila* (Test Product) significantly reduced IBS-SSS scores compared to baseline and outperformed both the Control Product and placebo.
- The Control Product (*B. lactis* + *L. plantarum*) also showed statistically significant improvements compared to placebo, confirming their known therapeutic value in IBS.
- The placebo group demonstrated no significant improvements, confirming the specific clinical benefits of probiotic interventions.

Quality of life (QOL)

- Both the Test and Control groups experienced marked improvements in QOL across multiple domains including abdominal discomfort, bowel function, and psychological well-being [9].
- *Akkermansia muciniphila* showed superior QOL benefits compared to the Control Product, indicating its broader therapeutic potential beyond symptom relief.

Scientific rationale

- *Akkermansia muciniphila* is a next-generation probiotic with a well-documented role in gut barrier enhancement, immune modulation, and anti-inflammatory effects, all of which are highly relevant in IBS pathophysiology [7].
- *Bifidobacterium lactis* and *Lactobacillus plantarum* are established strains with demonstrated benefits in gastrointestinal health and SCFA production [10], though *A. muciniphila* may offer additional advantages due to its unique mucin-degrading activity and host-microbiota interaction capabilities [4].

Safety and tolerability

- All probiotic formulations were well-tolerated, with only mild to moderate adverse events reported and no significant differences among groups.
- Clinical laboratory tests and vital signs remained within normal limits throughout the study, supporting the favourable safety profile of all tested strains, including *A. muciniphila*.

Placebo-controlled rigor

- The use of a placebo arm added strength to the study design by confirming that observed improvements were due to specific probiotic effects rather than placebo responses.
- This aligns with broader scientific consensus emphasizing strain-specific, well-controlled trials for evaluating probiotics in functional gastrointestinal disorders [15].

Limitations

- The study's sample size (n = 90) provides important preliminary data but limits generalizability.
- The duration and single-centre design necessitate further multicentre and long-term trials to validate and expand upon these findings.

The findings from this clinical trial suggest that *Akkermansia muciniphila* is a highly effective and safe probiotic for managing irritable bowel syndrome, showing superior symptom relief and quality of life improvements compared to both a placebo and a combination of two widely used probiotic strains (*B. lactis* and *L. plantarum).* The safety profile of *A. muciniphila* is consistent with its status as an emerging, next-generation probiotic. These results not only reinforce the therapeutic potential of targeted microbiome modulation in IBS but also highlight the need for continued research into novel probiotic strains, their mechanisms of action, and long-term clinical benefits. The study provides a scientifically robust foundation for considering *Akkermansia muciniphila* as a clinically relevant option in IBS management and a candidate for inclusion in evidence-based probiotic guidelines. Further investigations involving larger cohorts, mechanistic studies, and microbiome profiling will be essential to fully harness its therapeutic promise in functional gastrointestinal disorders.

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