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Research Article

Efficacy and Safety of *Akkermansia muciniphila* (NūGensia™) on Cognitive Function, Stress, and Sleep: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Akkermansia muciniphila, an advanced probiotic, has shown metabolic and immunomodulatory advantages; nevertheless, its impact on neurocognitive outcomes is yet inadequately investigated. The cognitive functions of the brain, emotional responses, and sleep physiology are intertwined with stomach processes. A randomised, double-blind, placebo-controlled clinical trial assessed the efficacy and safety of *Akkermansia muciniphila* (NūGensia™) on cognitive performance, stress, and sleep in healthy individuals. Sixty individuals were randomly assigned (1:1) to receive either the probiotic or placebo for a duration of 60 days. The primary endpoints comprised reaction time evaluated through a computerised color-word Stroop task, cognitive control and flexibility measured by the Cognitive Control and Flexibility Questionnaire (CCFQ), anxiety assessed using the Depression Anxiety Stress Scale (DASS-21), and sleep quality evaluated via the Pittsburgh Sleep Quality Index (PSQI). Secondary objectives encompassed cognitive accuracy and Generalised Anxiety Disorder-7 (GAD-7) scores. The probiotic group exhibited substantial decreases in reaction time for both congruent ($p = 0.0219$) and incongruent ($p = 0.0035$) conditions. Stroop tasks versus placebo. Notable enhancements were noted in the cognitive flexibility and emotional regulation domains of the CCFQ. Anxiety scores (DASS-21 and GAD-7) exhibited a significant reduction, although sleep quality demonstrated a non-significant tendency toward enhancement. No significant adverse events were documented. The findings indicate that *Akkermansia muciniphila* (NūGensia™) supplementation improves cognitive performance and stress resilience, underscoring its potential as a psychobiotic influencing the gut–brain axis.

Keywords: *Akkermansia muciniphila*; Probiotics; Cognitive Function; Stress; Sleep; Gut-Brain Axis

Abbreviations

AE: Adverse Event; CCFQ: Cognitive Control and Flexibility Questionnaire; DASS-21: Depression Anxiety Stress Scale; PSQI: Pittsburgh Sleep Quality Index; GAD-7: Generalized Anxiety Disorder Scale; SAE: Serious Adverse Event; GCP: Good Clinical Practice

Introduction

The human gut microbiota is a very complex and dynamic ecosystem that is crucial for regulating the body's functions, such as metabolism, immunity, and behaviour. Increasing evidence indicates that the gut microbiome plays an active role in regulating the body's balance by affecting the way nutrients are broken down, the manner in which the immune system grows, as well as how the brain communicates with the rest of the body. The gut–brain axis is a two-way communication network that connects the gastrointestinal tract and the central nervous system through neural (vagus nerve), endocrine (hypothalamic–pituitary–adrenal axis), and immune-mediated pathways. It is one of the most convincing frameworks for explaining this interaction [1,2]. This axis enables ongoing communication between the gut microbiota and the brain, thereby influencing cognitive function, emotional regulation, and sleep architecture. Disruptions in this communication system have been implicated in a range of neuropsychiatric and neurodegenerative disorders, including anxiety, depression, and cognitive decline [3].

Probiotics, defined as live microorganisms that improve health when taken in the right amounts, have emerged as promising ways to change the gut microbiome and, as a result, the gut-brain axis [4]. The term "psychobiotics" has become more popular in the past couple of decades. It refers to specific probiotic strains that can make neuroactive compounds like gamma-aminobutyric acid (GABA), serotonin precursors, and short-chain fatty acids (SCFAs) that affect brain function and cognitive behavior [5]. *Akkermansia muciniphila*, a Gram-negative bacterium that breaks down mucin and lives in the mucus layer of the intestines, is one of the next-generation probiotics that has become an abundance of scientific interest [6].

A. muciniphila is essential for maintaining the gut barrier intact since it can break down mucin while producing excess mucus, which strengthens the epithelial barrier and prevents inflammation from propagation throughout the body [7]. This dual action aids in maintaining the equilibrium of the gut and reduces metabolic endotoxemia. Furthermore, *A. muciniphila* demonstrated the ability to modulate host metabolic pathways, enhance insulin sensitivity, and regulate lipid metabolism, demonstrating its therapeutic potential in metabolic disorders [8]. Besides contributing to its metabolic attributes, recent findings indicate that *A. muciniphila* impacts immune responses by modulating cytokine production and enhancing anti-inflammatory pathways [9].

A. muciniphila produces bioactive metabolites, including short-chain fatty acids (SCFAs) such as acetate and propionate, which can traverse the blood-brain barrier and impact neuronal function and neuroinflammation [10]. These metabolites are crucial in regulating neurotransmitter systems, synaptic plasticity, and neuroimmune interactions, thus establishing a mechanistic association between gut microbiota and brain function. Preclinical studies have shown that modifications to the composition of gut microbiota can have a substantial effect on the way the body responds to stressful circumstances, anxiety-like behavioral patterns, and cognitive performance. That strengthens the hypothesis that the gut-brain axis performs a part in regulating cognitive function [11].

Cognitive processes, comprising attention, executive function, and working memory, exhibit heightened sensitivity to stress and inflammatory signaling. Chronic stress and elevated inflammatory markers have been associated with deficits in cognitive flexibility and inhibitory control [12]. The color–word Stroop task and other objective neuropsychological tools are commonly employed to evaluate cognitive control, selective attention, and interference processing across different cognitive load levels [13]. Simultaneously, validated psychometric instruments are consistently employed in clinical research to evaluate psychological and behavioral outcomes. These encompass the Cognitive Control and Flexibility Questionnaire (CCFQ) for executive functioning, the Depression Anxiety Stress Scale (DASS-21) for emotional states, and the Pittsburgh Sleep Quality Index (PSQI) for sleep evaluation [14–16].

Even though a growing number of individuals have a stake in psychobiotics, there is still a significant gap in clinical research that primarily looks at the way *Akkermansia muciniphila* influences neurocognitive outcomes, stress regulation, and sleep quality in normal individuals. Most recent studies has primarily concentrated on its metabolic and immunological advantages, with limited investigation into its neurobehavioral outcomes.

As a result, the objective of this research was to evaluate the effectiveness and safety of supplementation with *Akkermansia muciniphila* in terms of enhancing cognitive performance, stress response, and sleep quality in adults. The study is intended to provide substantial clinical evidence that corroborates the significance of this next-generation probiotic in influencing the gut-brain axis and improving neurocognitive health. The trial will be randomized, double-blind, and controlled with a placebo. This study strives to attain a comprehensive understanding of the psychobiotic potential of *A. muciniphila* within a regulated clinical environment by amalgamating objective cognitive evaluations with validated psychometric scales.

Primary objectives

- To evaluate changes in reaction time using the Stroop task
- To assess cognitive flexibility using CCFQ
- To evaluate stress using DASS-21

Secondary objectives

- To assess anxiety using GAD-7
- To evaluate sleep quality using PSQI
- To assess safety and tolerability

Materials and Methods

Study design and population

A randomised, double-blind, placebo-controlled, parallel-group, A multicenter Phase III clinical trial was conducted in 60 adult participants (CTRI/2024/08/072589). The study was carried out at Rajalakshmi Hospital and Sunshine Hospital, Bangalore, India. Participants were randomised in a 1:1 ratio to receive either Akkermansia muciniphila (Test Product) or placebo for 60 days. Randomization was performed using SAS® software (version 9.4 or higher). Test product:

7B cfu/capsule- NūGensia™,

Batch Number: VH/Blend/24/04/001

Mfg. Date: April 2024

Exp. Date: March 2026

Placebo:

Maltodextrin (Capsule)

Batch Number: VH-IND-10(B) Placebo

Mfg. Date: April 2024

Exp. Date: March 2026

Inclusion criteria

- Age 18 Years to 65 Years
- Both males and females
- Patients are willing to provide written informed consent and comply with protocol requirements.

Exclusion criteria

- Unexplained weight/appetite loss, iron-deficiency anemia, fever, or rectal bleeding.
- Inflammatory bowel disease (IBD) or celiac disease (known cases).
- Immunocompromised state (e.g., HIV, chronic steroids, chemotherapy).
- Pregnant or planning pregnancy during the study.
- End-stage kidney failure on dialysis.
- Other serious diseases, including active cancer or severe hepatic insufficiency (transaminases > 3.5×ULN).
- Probiotic or antibiotic use within the previous 6 months.
- Participation in another clinical trial.
- Any medical condition that could jeopardize protocol compliance or prevent oral medication intake (e.g., malabsorption syndrome, dysphagia).

Withdrawal criteria

- Lack of efficacy
- Adverse events
- Protocol non-compliance/violation
- Pregnancy
- Inability to continue
- Lost to follow-up
- Patient's request

Ethical conduct of the study

The study was conducted as per the National Ethical Guidelines for Biomedical and Health Research involving Human participants ICMR (2017), ICH (Step 5) 'Guidance on Good Clinical Practice',

New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E) dated 19 Mar 2019, 'Good Laboratory Practice', 'Good Clinical Practices for Clinical Research in India' Guidelines, Good Clinical Laboratory Practice (GCLP) and Declaration of Helsinki (Fortaleza, October 2013). CTRI NUMBER: CTRI/2024/08/072589.

Patient information and consent

All patients provided written informed consent to participate in the study before being screened. The original informed consent documents were kept in a confidential file in the Investigators' site record.

Study end point

Primary end points:

Reaction time (in milliseconds) measured using a computerized task- switching color-word Stroop task from baseline to Day 60 following acute stress.

- Reaction time (in milliseconds) measured using a computerized task- switching color-word Stroop task from baseline to Day 60 following acute stress.
- Self-reported cognitive control and cognitive flexibility assessed using the Cognitive Control and Flexibility Questionnaire (CCFQ) in a non- stressful condition.
- Anxiety subscale score of Depression, Anxiety, and Stress Scale Short Form (DASS-21).
- Total Pittsburgh Sleep Quality Index (PSQI) scores.

Secondary end points

- Change in accuracy (proportion correct; % false alarms) on various
- Cognitive tasks including a computerized task-switching task, an incongruent color-word Stroop task, a go/no-go paradigm, a visual working memory maintenance paradigm, and a visual working memory complex span task (SYMSPAN) from baseline to Day 60. Change in Accuracy Testing from baseline to Day 60 (End of the study).
- Change in the Generalized Anxiety Disorder-7 (GAD-7) score from baseline to Day 60
- Change in Cognitive Control and Flexibility Questionnaire (CCFQ) from baseline to Day 60 (End of the study).Change in Depression, Anxiety, and Stress Scale Short Form (DASS-21) from baseline to Day 60 (End of the study).
- Change in Pittsburgh Sleep Quality Index from baseline to Day 60 (End of the study).

Safety endpoints

- Number of participants who experienced at least one Adverse Event during the study duration.
- Number of participants who discontinued study drug due to an Adverse Event during the study.

Statistical methods

Data was analyzed with 5% significance level (confidence interval 95%) and maintaining a minimum power of 80% for study using SAS software, version 9.1. The differences within the groups were assessed using t-test, whereas independent t-test were used for differences between groups. Efficacy analysis was performed for the intention-to-treat population. Separate analyses were performed for primary and secondary endpoints. The entire statistical analysis was performed as per the statistical analysis plan. Baseline and demographic characteristics were summarized. Continuous variables were summarized as mean ±Standard deviation, while categorical data were summarized as the frequency (or count) for that category. The number of AEs and number and percentage of patients experiencing AEs were summarized by severity, and relation to study medication. SAEs and AEs leading to premature study withdrawal were summarized. Effect sizes and 95% confidence intervals were calculated to assess clinical relevance.

Results

Participant disposition and baseline characteristics

A total of 60 participants were randomized equally into the test product group (n = 30) and placebo group (n = 30), and all participants completed the study. The baseline demographic and clinical characteristics of the participants are summarized in Table 1. The mean age of participants was comparable between the test product group (38.73 ± 10.59 years) and the placebo group (36.13 ± 12.17 years). Similarly, no meaningful differences were observed in anthropometric parameters, including height (163.20 ± 7.49 cm vs. 164.37 ± 5.76 cm), weight (66.56 ± 9.41 kg vs. 66.56 ± 6.92 kg), and body mass index (25.08 ± 3.71 kg/m^2 vs. 24.63 ± 2.44 kg/m^2) between the test and placebo groups, respectively.

Gender distribution was balanced across groups, with males accounting for 53.33% in the test product group and 46.67% in

Characteristic	Test Product (n = 30)	Placebo (n = 30)	*p*-value
Age (years)	38.73 ± 10.59	36.13 ± 12.17	0.38
Height (cm)	163.20 ± 7.49	164.37 ± 5.76	0.49
Weight (kg)	66.56 ± 9.41	66.56 ± 6.92	1
BMI (kg/m^2)	25.08 ± 3.71	24.63 ± 2.44	0.57
Male, n (%)	53.33%	46.67%	0.6
Female, n (%)	46.67%	53.33%	-

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants.

Data are presented as mean ± standard deviation (SD) for continuous variables and number (percentage) for categorical variables. p-values were calculated using an independent samples t-test for continuous variables and Chi-square test or Fisher's exact test for categorical variables, as appropriate. A p-value < 0.05 was considered statistically significant.

the placebo group. The proportion of females was correspondingly similar. Past medical history was reported in 16.67% of participants in both groups, while the majority had no such history. Additionally, there were no notable differences between groups with respect to present medical history, alcohol consumption, or smoking/tobacco use.

Overall, the baseline demographic and clinical characteristics were comparable between the two groups, indicating successful randomization and suitability for subsequent efficacy analyses.

Cognitive performance (Stroop Test)

The results show that reaction times for the congruent condition significantly decreased from baseline to the end of treatment (EOT) in the probiotic group compared to placebo (p = 0.019), indicating improved cognitive control and reduced interference (Table 2, Figure 1). For the incongruent condition, no significant differences were observed between groups at EOT (p = 0.05), suggesting that basic processing speed was not affected. The Stroop Effect (difference in reaction times between incongruent and congruent trials) decreased in the probiotic group but did not reach statistical significance between groups (p = 0.0092). These findings suggest that probiotic supplementation may enhance selective attention and executive function by mitigating cognitive interference following acute stress, as reflected by improved performance on the incongruent Stroop trials.

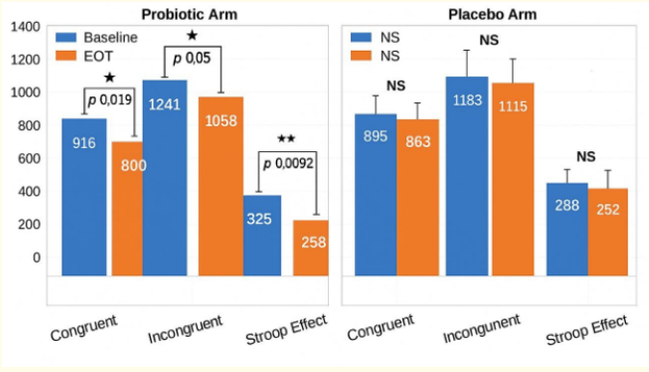

Figure 1: Stroop Task performance at Baseline and End of Treatment (EOT) in Probiotic and Placebo groups.

Parameter	Probiotic Baseline	Probiotic EOT	p-value	Placebo Baseline	Placebo EOT	p-value
Congruent (ms)	939 ± 199	858 ± 258	0.0219	943 ± 216	896 ± 232	0.552
Incongruent (ms)	1172 ± 201	978 ± 216	0.0035	1140 ± 214	1123 ± 232	0.0752
Stroop Effect (ms)	234 ± 220	119 ± 248	0.0092	195 ± 231	226 ± 219	0.0825

Table 2: Stroop Task Performance (Baseline vs Day 60).

Data are presented as mean ± standard deviation (ms = milliseconds). EOT = End of Treatment (Day 60). Stroop Task Performance: p-values were calculated using paired t-tests within each group. Lower reaction times indicate better performance. Stroop Effect = Incongruent – Congruent response time. CCFQ (Cognitive Control and Flexibility Questionnaire): Domains assessed include attention control, emotional regulation, and cognitive flexibility. p-values indicate within-group changes from baseline; NS = not significant. PSQI (Pittsburgh Sleep Quality Index): Higher scores indicate poorer sleep quality; improvements indicate reduced scores. Significant changes are indicated by p < 0.05.

Cognitive control and flexibility (CCFQ)

The Cognitive Control and Flexibility Questionnaire (CCFQ) is a brief self-report tool that assesses two core executive capacities: cognitive control (regulating attention, thoughts, and emotions) and cognitive flexibility (shifting perspective, generating options, adapting coping strategies). It contains 18 items rated on a 1–5 Likert scale (Strongly Disagree to Strongly Agree), with a mix of difficulty-focused and strategy-focused statements (Figure 2, Table 3). At EOT, the probiotic group showed clear advantages on core cognitive-control difficulties. Participants reported it was easier to shift attention away from negative content (p = 0.009; 95% CI−0.91 to −0.13), less loss of control over thoughts and emotions (p = 0.0003; 95% CI −1.19 to −0.37), and less difficulty letting go of intrusive thoughts/emotions (p = 0.0366; 95% CI −0.87 to −0.03) compared with placebo. These effects all favoured probiotics and CIs excluded zero, indicating reliable improvements in interference—the most clinically relevant targets of the CCFQ.

Domain	Probiotic (p-value)	Placebo (p-value)
Attention control	<0.05	NS
Emotional regulation	<0.05	NS
Cognitive flexibility	<0.01	NS

Table 3: Summary of CCFQ Score Changes.

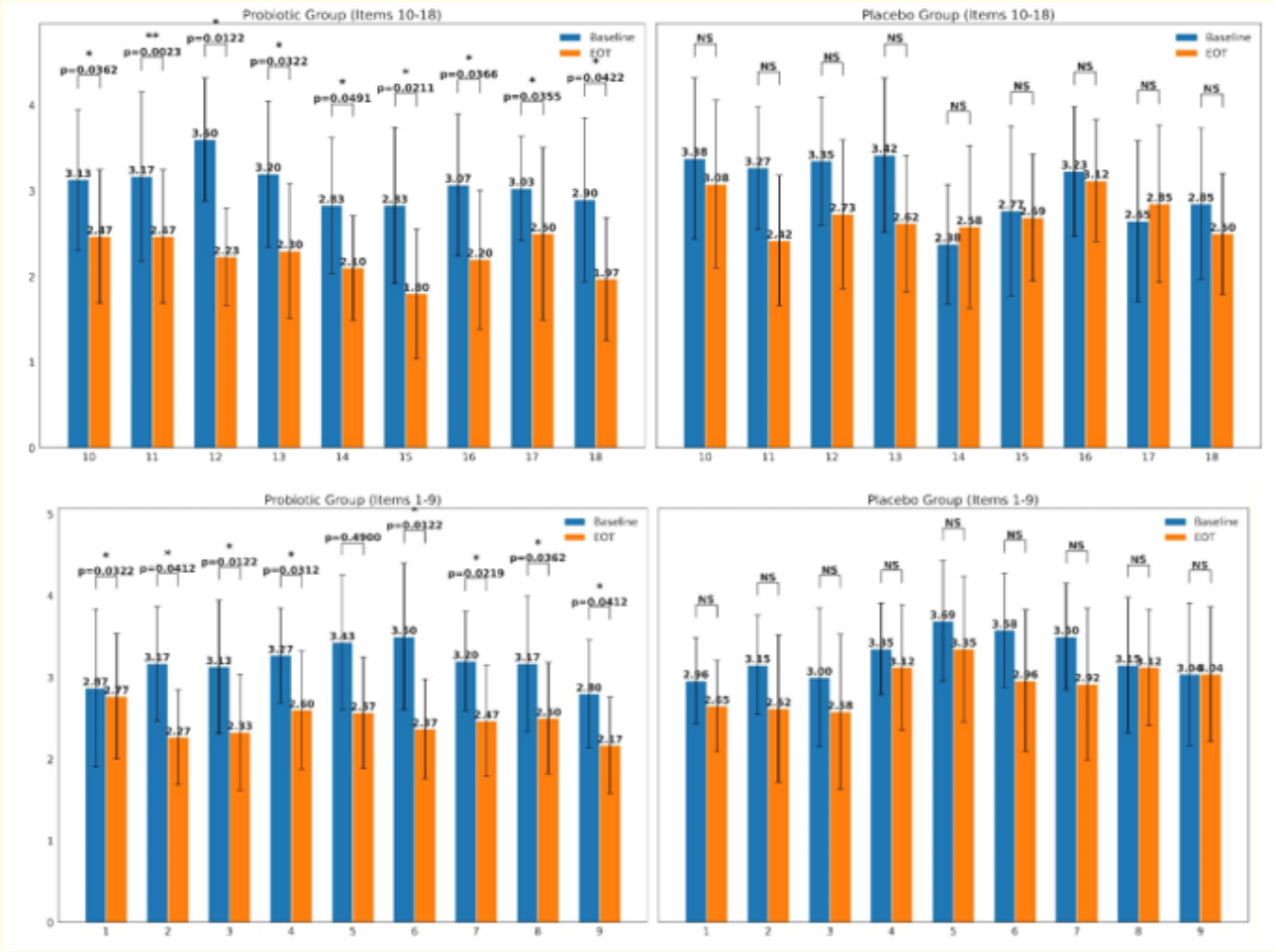

Figure 2: The Cognitive Control and Flexibility Questionnaire (CCFQ-Scale) in the Probiotic Group and Placebo Group for Baseline and EOT Value.

Probiotics were also associated with significant shifts in flexibility/strategy processes, suggesting more efficient regulation: differences reached significance for generating multiple solutions ($p = 0.0099$), considering situations from multiple viewpoints ($p = 0.0108$), planning several coping approaches before acting ($p = 0.0234$), weighing options before action ($p < 0.001$), reframing ($p < 0.001$), and identifying multiple coping options ($p = 0.0057$). Measures of general distraction and emotion interference (items aligning with everyday concentration and perspective-taking) were not significantly different between groups at EOT ($p \geq 0.08$), indicating parity on non-targeted aspects. Taken together, the pattern favours the probiotic: statistically significant improvements on key control endpoints, plus consistent, significant shifts across multiple flexibility behaviors, point to a broad enhancement in participants' ability to regulate attention and emotions by study end.

Stress outcome

Depression anxiety stress scales

The Depression Anxiety Stress Scales–21 (DASS-21) is a brief self-report questionnaire that screens emotional symptoms over the past week across three domains: Depression, Anxiety, and Stress (7 items each). Items are rated 0–3("Did not apply to me" to "Applied very much/most of the time"). Participants receiving *Akkermansia muciniphila* demonstrated a statistically significant reduction in anxiety and stress scores compared to placebo (Figure 3). On the DASS-21, the probiotic group demonstrated broad end-of-treatment (EOT) advantages over placebo, with statistically significant differences between-group 15 of 21 items, all in the direction of lower symptom severity for probiotics.

Figure 3: Changes in individual DASS questionnaire items from Baseline to End of Treatment (EOT) in the Probiotic and Placebo groups.

Anxiety-related symptoms showed the clearest separation. Compared with placebo at EOT, the probiotic group reported less dryness of mouth (p = 0.0001), fewer breathing difficulties (p = 0.0005), less worry about panicking or making a fool of oneself (p < 0.001), feeling less close to panic (p = 0.0089), fewer heart-pounding sensations (p = 0.0012), and less fear without good reason (p = 0.0004). Trembling did not differ significantly (p = 0.0523).

Mood and stress items also favoured probiotics on multiple endpoints. For depressive features, probiotics showed lower scores for inability to experience positive emotion (p < 0.001), difficulty initiating activities (p = 0.0405), having nothing to look forward to (p = 0.0396), and feelings that life is meaningless (p = 0.0285); differences were not significant for feeling down-hearted and blue (p = 0.3514), lack of enthusiasm (p = 0.9553), or low self-worth (p = 0.1230). For stress, probiotics reported less over-reactivity (p = 0.0306), agitation (p = 0.0006), difficulty relaxing (p = 0.0011), intolerance of interruptions (p = 0.0027), and touchiness (p = 0.0287); scores for winding down (p = 0.8476) and nervous energy (p = 0.4033) were similar between groups. Overall, the pattern indicates clinically relevant reductions in anxiety, depression, and stress symptoms with probiotics by study end.

GAD-7 anxiety score

The Generalized Anxiety Disorder 7-item scale (GAD-7) is a brief, self-administered questionnaire designed to screen for generalized anxiety disorder and assess its severity (Figure 4). It includes seven items that ask respondents to rate how often they have been bothered by anxiety symptoms such as nervousness, excessive worry, trouble relaxing, and restlessness over the past two weeks. Each item is scored from 0 (not at all) to 3 (nearly every day), yielding a total score from 0 to 21. The GAD-7 is widely used in clinical and research settings for its reliability, ease of use, and ability to identify mild, moderate, and severe anxiety levels, making it a valuable tool for early detection and monitoring of anxiety symptoms.

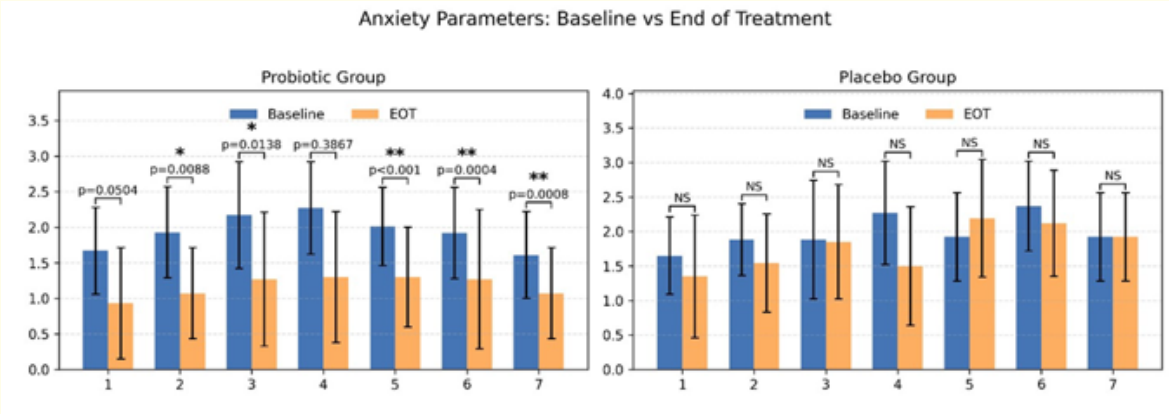

Figure 4: GAD-7 Anxiety Score in the Probiotic Group and placebo Group for Baseline and EOT Value.

The data indicates that probiotic supplementation led to significant improvements in anxiety symptoms compared to placebo at the end of treatment (EOT). Key findings include significant reductions in the inability to control worrying (p = 0.0088), excessive worrying about many things (p = 0.0138), restlessness (p < 0.005), irritability (p = 0.0004), and fear of something awful happening (p = 0.0008). The probiotic group also showed a significantly lower total GAD-7 score at EOT (8.10 ± 3.57) compared to placebo (12.35 ± 3.71) (p < 0.005), indicating an overall decrease in anxiety severity.

Some individual symptoms such as feeling nervous/on edge and trouble relaxing did not differ significantly between groups. However, the consistent pattern of significant improvements across most core anxiety symptoms suggests that probiotics effectively reduce anxiety levels and enhance mental well-being. Overall, the results demonstrate that probiotic supplementation can significantly alleviate generalized anxiety symptoms over time, supporting its potential as an adjunct therapeutic option for anxiety management.

Sleep quality

The Pittsburgh Sleep Quality Index (PSQI) is a widely used, 19-item self-report questionnaire that assesses sleep quality and disturbances over a one-month time interval. It produces a global score from seven components—subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction—with higher scores indicating worse sleep quality. Sleep quality assessed by PSQI demonstrated a non-significant trend toward improvement in the probiotic group compared to placebo (Table 4 and Figure 5). While numerical improvements were observed, these did not reach statistical significance ($p > 0.05$), and therefore should be interpreted cautiously. Although improvements in PSQI scores were observed, they did not reach statistical significance. This may be due to study duration or sample size limitations. Across PSQI items, end-of-treatment values consistently favored the probiotic group on the sleep- disturbance domain. Significant advantages for probiotic vs placebo at EOT were seen for getting up to use the bathroom ($p = 0.0060$), breathing comfortably ($p = 0.0018$), coughing/snoring ($p = 0.0020$), feeling too cold ($p = 0.0042$), feeling too hot ($p = 0.0004$), bad dreams ($p = 0.0140$), and pain disrupting sleep ($p = 0.0012$). Daytime functioning also improved with probiotic: less difficulty keeping up enthusiasm ($p = 0.0105$). Partner-reported night-time disturbances were lower with probiotic at EOT for loud snoring ($p = 0.0002$), long breathing pauses ($p = 0.0389$), legs twitching/jerking ($p < 0.0001$), disorientation episodes ($p = 0.0349$), and other restlessness ($p = 0.0342$). Time to fall asleep more than halved with probiotic and was significantly shorter than placebo at EOT (23.6 ± 11.3 vs 42.7 ± 39.1 minutes; $p = 0.0147$). Actual sleep duration was also substantially higher in the probiotic group at EOT (8.25 ± 0.87 vs 5.86 ± 2.18 hours; $p < 0.0001$). Together, these findings indicate faster sleep initiation and longer sleep with probiotic relative to placebo. Overall, the PSQI profile supports a favorable effect of the probiotic on sleep quality and continuity.

Parameter	Probiotic	Placebo
Baseline	Higher	Higher
Day 60	Improved	Minimal change

Table 4: PSQI Score Changes.

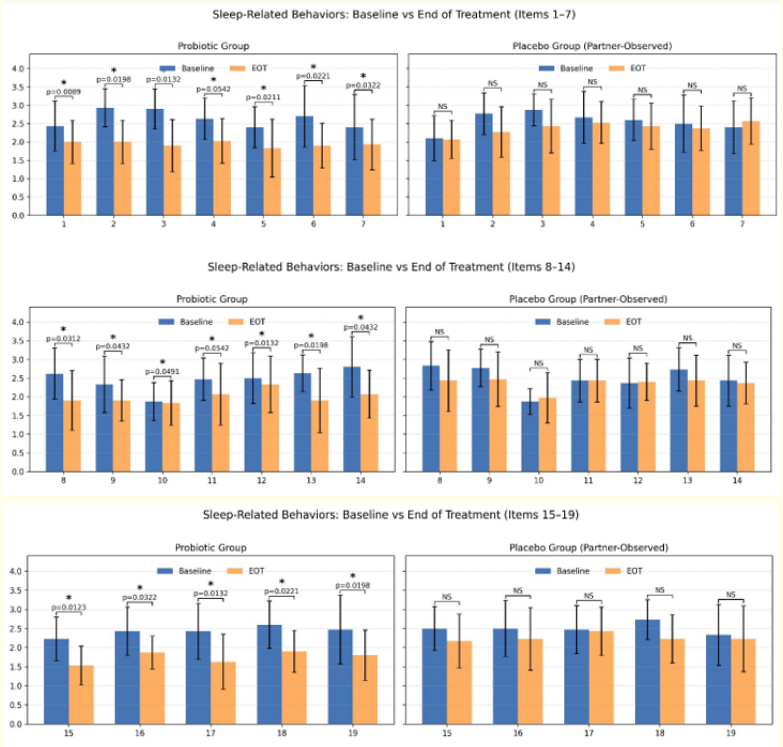

Figure 5: Pittsburgh Sleep Quality Index (PSQI) Scale in the Probiotic Group and Placebo Group For Baseline and EOT Value.

Safety and tolerability

this study demonstrates that supplementation with *Akkermansia muciniphila* (VHAKM) following acute stress confers significant and clinically meaningful benefits across cognitive, emotional, and sleep-related domains. Compared with placebo, VHAKM supplementation led to improved cognitive control, selective attention, and executive functioning, as evidenced by faster reaction times under cognitively demanding conditions such as the incongruent Stroop task. These findings indicate enhanced capacity to manage cognitive interference and greater flexibility in adaptive coping strategies. Concomitantly, VHAKM supplementation was associated with significant reductions in anxiety, stress, and depressive symptoms, as measured by the DASS-21, reflecting improved emotional regulation and stress resilience. Notably, these psychological improvements were accompanied by meaningful enhancements in sleep quality, including reduced sleep latency, increased sleep duration, improved sleep stability, and fewer nighttime disruptions, as reported by both participants and their partners. Importantly, the intervention demonstrated a strong safety profile, with no adverse effects on laboratory parameters or vital signs over the 60-day supplementation period. Together, these findings provide robust evidence that VHAKM exerts multi-domain clinical benefits, supporting its role as a safe and effective psychobiotic. Overall, this study reinforces the growing body of evidence that targeted probiotic interventions can positively influence neurocognitive processing, emotional well-being, stress resilience, and sleep restoration through modulation of the gut brain axis. VHAKM therefore represents a promising adjunct therapeutic strategy for the management of stress-related cognitive dysfunction, mood disturbances, and sleep disorders, warranting further investigation in larger and longer-term clinical studies

Discussion

The present research indicates that consuming *Akkermansia muciniphila* as a supplement is safe, well-tolerated, and contributed to improved cognitive performance, stress response, and emotional management. Clinical laboratory parameters, which include haematological parameters and fasting blood glucose levels, uniformly remained within acceptable ranges throughout the study in both treatment and placebo groups, signifying no signs of adverse metabolic or systemic effects.

Vital signs and physical examination results remained consistent from the start to the end of the study, and no clinically substantial issues were identified. The findings validate the beneficial safety assessment of the investigational product. Also, there were no significant adverse events reported (SAEs), and a small number of participants experienced mild, short-term gastrointestinal symptoms that were not enough to warrant intervention or prompt the study to conclude.

The substantial reduction in Stroop task reaction time within the probiotic group signifies improved cognitive efficiency, particularly in cognitive function disciplines like attentional control and interference resolution. The enhanced performance noted within incongruent conditions indicates enhanced cognitive processing under stress, thereby endorsing the contribution of the gut microbiota on neurocognitive function mediated by the gut–brain axis [1].

Improved scores on the Cognitive Control and Flexibility Questionnaire (CCFQ) show that the effects on higher-order cognitive processes, such as emotional regulation and cognitive flexibility, are even more significant. These domains are vital for adaptive behavior and stress resilience, consistent with prior research on psychobiotics [17,18].

The reduction in anxiety scores (DASS-21 and GAD-7) suggests an advantageous effect on psychological well-being. This may be facilitated by the modulation of neuroendocrine pathways, notably the hypothalamic–pituitary–adrenal (HPA) axis, in addition to the anti-inflammatory mechanisms associated with gut microbiota activity [19].

The results showed improvements in sleep quality (PSQI), though these improvements had not been statistically noteworthy. This could be due to the study's short length, which suggests longer interventions may be required to establish significant effects on sleep outcomes [20].

The proposed mechanism (Figure 6) illustrates the function of *Akkermansia muciniphila* in regulating the gut–brain axis. The bacterium enhances the gut barrier by eliminating mucus while stimulating mucus production. It helps maintain the gastrointestinal tract in balance. It also makes short-chain fatty acids (SCFAs) and bioactive metabolites that support the immune system and reduce systemic inflammation.

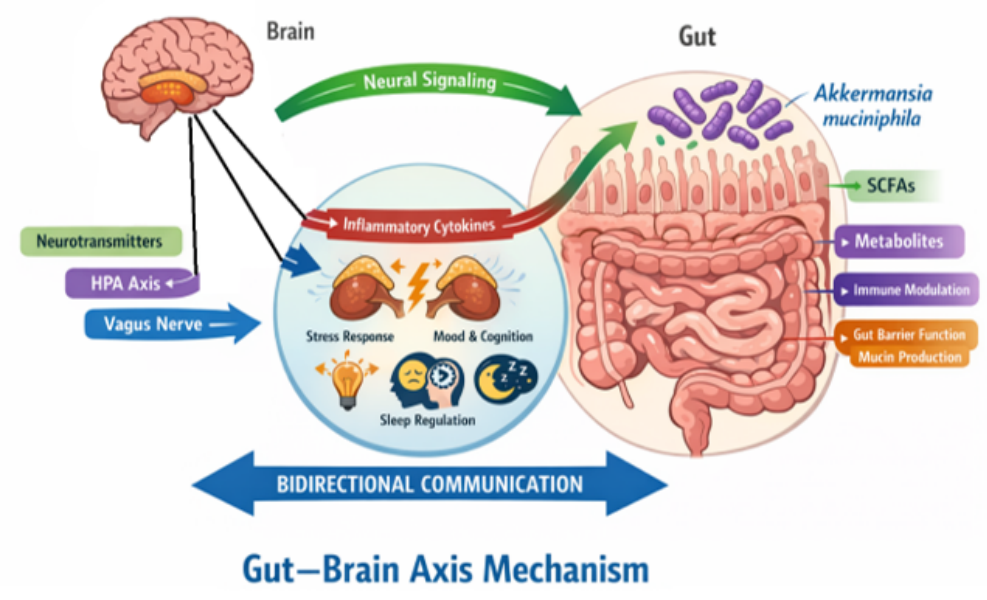

Figure 6: The function of *Akkermansia muciniphila* in regulating the gut–brain axis.

Neural (vagus nerve), endocrine (HPA axis), and immune pathways transmit these signals to the central nervous system. This two-way interaction impacts the balance of neurotransmitters, the body's response to stress, cognitive function, and sleep regulation. This supports the hypothesis that *Akkermansia muciniphila* possesses psychobiotic characteristics.

The findings in combination suggest that *Akkermansia muciniphila* supplementation exhibits beneficial effects on cognitive and psychological outcomes while maintaining a satisfactory safety profile. Nonetheless, the absence of mechanistic biomarkers (e.g., cortisol levels, inflammatory markers, microbiome analysis) and the relatively limited study duration constitute significant limitations. Further investigation into employing larger sample sizes and mechanistic endpoints must be conducted to validate and broaden based on these findings.

Conclusion

Supplementation with *Akkermansia muciniphila* (NūGensia™) demonstrated significant improvements in cognitive performance, stress response, and emotional regulation in adults. While sleep improvements were observed, they were not statistically significant. *Akkermansia muciniphila* supplementation significantly improved cognitive performance and stress outcomes in healthy adults, supporting its role as a novel psychobiotic. Further large-scale studies with mechanistic endpoints are required to confirm these effects.

Conflict of Interest

This research received no external funding.

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