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Assessment of *Akkermansia muciniphila* (Nugensia™) for Improving Clinical and Microbiological Outcomes in Women with Urinary Tract Infections

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Abstract

Recurrent urinary tract infections (UTIs) are common among women and frequently result in repeated antibiotic exposure, highlighting the need for non-antibiotic preventive strategies. This randomized, double-blind, placebo-controlled, parallel, multicenter study evaluated the efficacy and safety of oral *Akkermansia muciniphila* VHAKM (Nugensia™) in women with recurrent UTI. Sixty participants were randomized 1:1 to receive *A. muciniphila* VHAKM (1×10^9 CFU/day) or placebo for 60 days. The reported mean number of symptomatic UTI episodes per participant was lower with *A. muciniphila* VHAKM than placebo (0.87 ± 0.73 vs. 1.32 ± 0.82; $p = 0.014$), and fewer participants experienced at least one symptomatic UTI (50.0% vs. 76.7%; $p = 0.031$). Culture-positive UTI, antibiotic use, and rescue-medication use were also significantly lower in the intervention group. Improvements in the Typical, Differential, and Quality-of-Life domains of the Acute Cystitis Symptom Score were significantly greater with *A. muciniphila* VHAKM than placebo (all $p < 0.05$). Following treatment, the intervention group showed lower measured levels of *Escherichia coli and Proteus mirabilis* and higher levels of *Bifidobacterium*, accompanied by a reduction in vaginal pH. No serious adverse events or treatment-related discontinuations were reported. These findings support further investigation of *A. muciniphila* VHAKM as a potential non-antibiotic strategy for reducing recurrent UTI and associated urogenital symptoms in women.

Keywords: *Akkermansia muciniphila VHAKM; Nugensia; Urinary Tract Infection; UTI; Probiotic*

Abbreviations

UTI: Urinary Tract Infection; ACSS: Acute Cystitis Symptom Score; FSH: Follicle Stimulating Hormone; LH: Luteinizing Hormone; CFU: Colony Forming Unit; qRT-PCR: Quantitative Real-Time Polymerase Chain Reaction; BV: Bacterial Vaginosis; AE: Adverse Event; SAE: Serious Adverse Event; CTRI: Clinical Trials Registry India

Introduction

Urinary tract infections (UTIs) are among the most common bacterial infections in women and represent an important cause of recurrent morbidity and antimicrobial use. Recurrence is particularly challenging, as repeated episodes frequently require additional courses of antibiotics and may contribute to alterations in the host microbiota and the emergence of antimicrobial resistance [1]. These

limitations have increased interest in complementary and non-antibiotic approaches for the prevention and management of recurrent UTI.

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [2]. Their biological effects may involve several mechanisms, including modulation of host immune responses, inhibition of pathogenic microorganisms, production of bioactive metabolites, and interactions with epithelial and mucosal barriers [2]. In addition to their local effects within the gastrointestinal tract, probiotics may influence host physiology through microbial metabolites and immune-mediated mechanisms, providing a rationale for investigating their effects beyond gastrointestinal health [3].

Among microorganisms of emerging interest, *Akkermansia muciniphila* is a mucin-degrading bacterium naturally present in the human gastrointestinal tract, where it primarily inhabits the intestinal mucus layer. Its ability to utilize mucin places *A. muciniphila* in close interaction with the intestinal epithelium and the mucosal environment [4]. The organism has received increasing attention because of its potential involvement in maintenance of intestinal barrier function, modulation of immune responses, and microbial and metabolic homeostasis [5]. These properties have led to growing interest in the potential application of *A. muciniphila* as a probiotic organism [6].

The relationship between the intestinal and urogenital microbial ecosystems may also be relevant to UTI susceptibility. Uropathogenic microorganisms can originate from gastrointestinal reservoirs and subsequently colonize the periurethral and urogenital environments [6]. At the same time, the composition of the vaginal microbiota represents an important component of urogenital health. A vaginal environment enriched in beneficial microorganisms, particularly *Lactobacillus* spp., is generally associated with an acidic pH and reduced colonization by potential uropathogens [7]. In contrast, disruption of this microbial environment may facilitate colonization by organisms commonly associated with UTI, including *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* [8,9].

These observations have supported investigation of probiotics as a potential strategy for recurrent UTI. Proposed mechanisms include competitive inhibition of pathogenic microorganisms, modulation of local and systemic immune responses, production of antimicrobial compounds, and alteration of microbial environments in ways that are less favorable to uropathogen persistence [10,11]. Previous studies of probiotics in recurrent UTI have primarily focused on *Lactobacillus* species, with clinical outcomes varying according to the strain, route of administration, and population evaluated [7,12]. The potential utility of *A. muciniphila* in this context, however, remains comparatively unexplored.

Given its established interaction with the intestinal mucosal environment and its proposed immunomodulatory and microbiota-modulating properties, oral supplementation with *A. muciniphila* may represent a potential approach for influencing clinical and biological parameters associated with recurrent UTI. However, clinical evidence evaluating this application remains limited. Therefore, the present randomized, double-blind, placebo-controlled, parallel, multicenter study evaluated the efficacy and safety of *Akkermansia muciniphila* VHAKM in women with recurrent UTI. The effects of supplementation were assessed through symptomatic UTI incidence and urogenital symptom scores, together with biological parameters including vaginal microbiota and vaginal pH and assessments of safety, hormonal, and reproductive parameters.

Objective of the Study

The primary objective of this study was to evaluate the effectiveness of *Akkermansia muciniphila* VHAKM on the clinical and biological parameters of women with urinary tract infection, while secondary objectives included evaluating the probiotic strain safety in the same subjects.

Materials and Methods

Ethical approval

The clinical study was conducted at Rajalakshmi Hospital & Research Centre, Bangalore, and Srinivasan Rajalakshmi Memorial Hospital, Chennai having CTRI number-CTRI/2024/08/072591. The trial was registered before enrollment began. The study received ethical approval from their respective Ethics Committees. The study protocol and the patient information sheet(s) were reviewed and approved by the appropriate Ethics Committee. The approvals were obtained prior to the initiation of the study and in compliance with the declaration of Helsinki (Brazil Assembly, 2013) and in compliance with the current ICH GCP Guidelines, and other applicable regulatory guidelines.

Study population and design

This randomized, double-blind, placebo-controlled study enrolled 60 adult women to evaluate the metabolic effects of a probiotic containing *Akkermansia muciniphila* VHAKM (Nugensia™) over 60 days. 88 women signed up for this study and were randomized by SAS. After reviewing exclusion criteria, 60 women were enrolled, and there were no dropouts. Eligible participants were randomly assigned a 1:1 ratio to receive either the test product or placebo (maltodextrin) according to a computer- generated randomization schedule produced using SAS software (Version 9.4 or higher, SAS Institute Inc., USA). The primary endpoints were changes from baseline to day 60 on incidence rate of symptomatic UTI, Acute Cystitis Symptom Score (ACSS) questionnaire, and change in vaginal microbiota. Secondary endpoints included changes in vaginal pH, hormonal and reproductive parameters (FSH, LH, serum estradiol levels, serum testosterone levels, antral follicle count, and ovarian volume) from baseline to day 60. For secondary objectives of safety, the endpoints were quantification of adverse events leading to discontinuation of the study or not. All investigators, study staff, and participants were blinded to treatment allocation for the duration of the trial. Efficacy and safety assessments were performed at baseline, days 14, 28, 45, and 60, with analyses conducted on the randomized population. Results were pooled from both test locations, and no site effects were assessed.

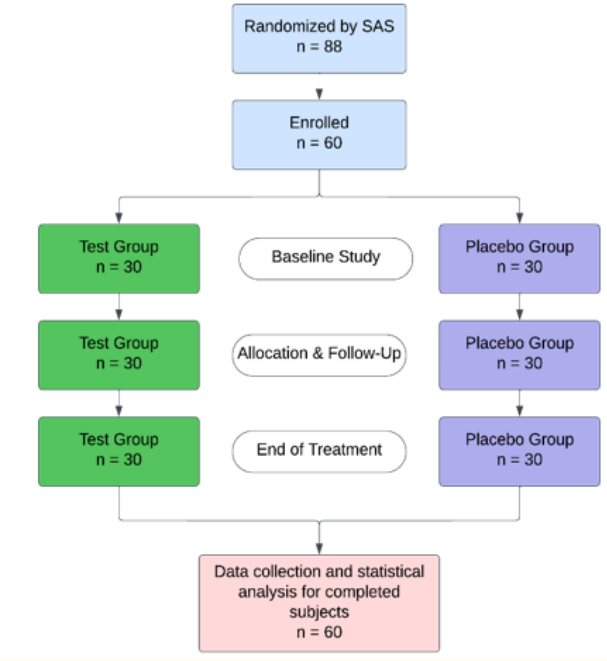

Figure 1: *Clinical trial study population, by taking into account study at baseline, follow-ups, and end of treatment.*

Eligibility criteria

Inclusion criteria

Eligible participants were females aged 18 - 70 years old, both pre- and post-menopausal, with a history of recurrent UTIs. Post-menopausal women were defined as having 12 months or more since their last period (natural or induced due to surgical or medical intervention), while recurrent UTIs were defined as 3 or more episodes in the past 12 months before beginning the study, of which two were approximately in the 6 months prior to the screening visit, and at least one must have been diagnosed medically and treated by a healthcare professional. Participants provided written informed consent and agreed to comply with all protocol procedures.

Exclusion criteria

Individuals were excluded for immunocompromising conditions, known allergies to investigational product or its excipients, known vaginal infection other than bacterial vaginosis (BV) or yeast infection at the time of screening, subjects who needed changes to medical intervention or in-office procedures in the prior 3 months, wore a pessary, used catheters regularly, had an obstruction or neurogenic bladder causing bladder emptying, had recent antibiotic use (30 days), significant acute or chronic co-existing illness, or medical conditions/diseases that may affect subject safety or confound study results, as judged by investigators.

Primary end points

The primary endpoints were the incidence rate of symptomatic UTI, acute cystitis symptom score (ACSS) questionnaire, and change in vaginal microbiota from baseline (first visit) to day 60.

Secondary end points

Secondary endpoints encompassed changes from baseline to day 60 in vaginal pH, follicle-stimulating hormone (FSH), luteinizing hormone (LH), serum estradiol levels, serum testosterone levels, antral follicle count, and ovarian volume.

Safety endpoints

Safety endpoints included the number of participants experiencing at least one adverse event (AE) over the study duration and the number discontinuing the study intervention due to an adverse event.

Study groups

Akkermansia muciniphila (Test product):

- *Akkermansia muciniphila* VHAKM (1 billion CFU/capsule)
- Batch number: VH/Blend/24/04/001.
- Mfg. date: April 2025.
- Exp. date: March 2027.
- Route of administration and dosage: One capsule having 1 billion CFU taken orally prior to a meal per day for 60 days.

Placebo product:

- Maltodextrin
- Name of the product: VH-IND 8-B (Placebo).
- Mfg. date: April 2025.
- Exp. date: March 2027.
- Route of administration and dosage: One capsule taken orally prior to a meal per day for 60 days.

Statistical analysis plan

Continuous variables were summarized as mean ± standard deviation (SD), and categorical variables were summarized as counts and percentages. Mean symptomatic UTI episodes per participant were compared between treatment groups using Welch's t-test. Distributional comparisons of participant-level UTI episode counts were performed using the Mann-Whitney U test. Categorical outcomes, including incidence of ≥1 symptomatic UTI, culture-positive UTI, antibiotic use, rescue-medication use, and adverse events, were compared using Fisher's exact test.

For ACSS domain scores, within-group changes from baseline to Day 60 were assessed using paired t-tests, and between-group differences in change-from-baseline values were tested by independent two-tailed t-test with Welch correction for unequal variances; baseline comparability was tested by independent t-test. Vaginal microbiota measures, vaginal pH, hormonal variables, and reproductive parameters were analyzed as continuous variables using Welch's t-tests for between-group comparisons; however, only descriptive results are presented for secondary endpoints. All tests were two-sided with statistical significance set at $p < 0.05$.

No multiplicity adjustment was prespecified. Accordingly, p-values for individual components of the ACSS, microbiota assessments, and secondary endpoints should be interpreted with consideration of the increased risk of Type l error associated with multiple hypothesis testing.

Results and Discussion

Sixty women with recurrent UTI were randomized in a 1:1 ratio to receive *Akkermansia muciniphila* VHAKM (n = 30) or placebo (n = 30) for 60 days. All randomized participants completed the study. The treatment groups were reported to be comparable with respect to baseline demographic and clinical characteristics. In particular, the historical frequency of UTI during the preceding 12 months was similar between groups (4.20 ± 1.30 episodes in the *A. muciniphila* VHAKM group and 4.17 ± 1.51 episodes in the placebo group).

Incidence of symptomatic urinary tract infection

During the 60-day intervention, the patient-reported mean number of symptomatic UTI episodes per participant was significantly lower in the *A. muciniphila* VHAKM group than in the placebo group (0.87 ± 0.73 vs. 1.32 ± 0.82 episodes/participant; p = 0.014, table 1; figure 2). Similarly, 50.0% of participants receiving *A. muciniphila* VHAKM experienced at least one patient-reported symptomatic UTI compared with 76.7% of participants receiving placebo (p = 0.031. table 1; figure 2).

Supportive infection-related outcomes were consistent with the primary analysis. Culture-positive UTI was reported in 46.7% of participants in the *A. muciniphila* VHAKM group and 73.3% of those receiving placebo (p = 0.037, table 1; figure 2). Antibiotic use during the study was also lower in the intervention group (50.0%) than in the placebo group (80.0%; p = 0.015, table 1; figure 2). Rescue medication was used by 20.0% and 40.0% of participants, respectively (p = 0.048). Collectively, these analyses indicated lower UTI-associated clinical and therapeutic burden among participants assigned to *A. muciniphila* VHAKM during the 60-day study period.

Parameter	*A. muciniphila*	Placebo	Between group p-value
Mean episodes per subject (± SD)	0.87 ± 0.73	1.32 ± 0.82	0.014
Total episodes	34	50	0.009
Subjects with ≥1 UTI, n (%)	15 (50.0%)	23 (76.7%)	0.031
Culture-positive UTI, n (%)	14 (46.7%)	22 (73.3%)	0.037
Antibiotic use, n (%)	15 (50.0%)	24 (80%)	0.015
Rescue medication, n (%)	6 (20.0%)	12 (40.0%)	0.048

Table 1: *Incidence of symptomatic UTI (baseline to day 60).*

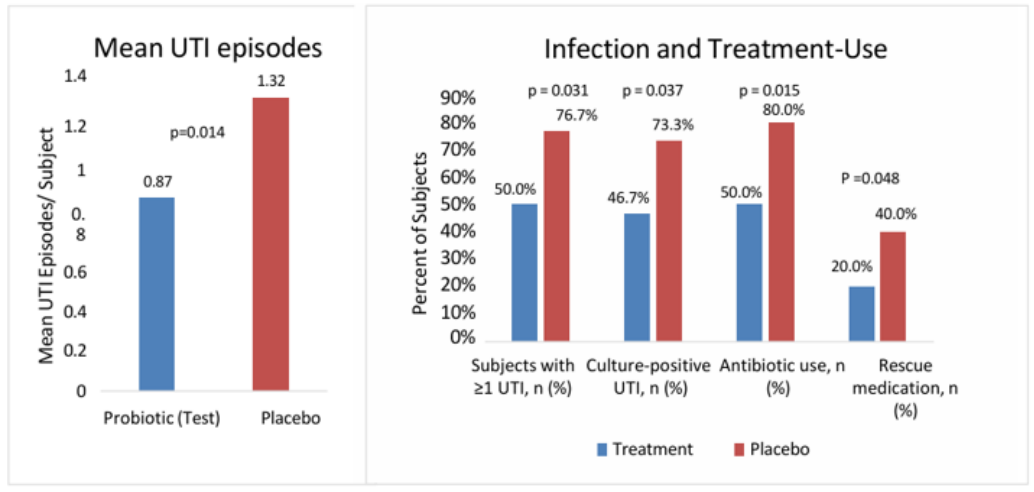

Figure 2: *Primary efficacy outcomes for UTI at Day 60. UTI episodes, UTI incidence, culture-positive UTI, antibiotic use, and rescue-medication use were lower in the probiotic group than in the placebo group. Significant differences were observed for UTI episodes (p = 0.014), ≥1 UTI (p = 0.031), and rescue-medication use (p = 0.048).*

Acute cystitis symptom score

Urogenital symptoms were evaluated using the three scored domains of the ACSS: Typical symptoms, Differential symptoms, and Quality of Life. Baseline scores were comparable between treatment groups. Scores decreased from baseline to day 60 in both groups, indicating improvement over time; however, the magnitude of improvement was significantly greater among participants receiving *A. muciniphila* VHAKM.

ACSS Domain	Group	n	Baseline Mean ± SD	Day 60 Mean ± SD	Change Mean ± SD	Within-group p-value	Between-group p-value
Typical	Probiotic	30	8.10 ± 3.10	3.80 ± 2.45	-4.30 ± 3.15	0.004	0.009
Typical	Placebo	30	7.97 ± 2.76	6.20 ± 3.30	-1.77 ± 2.10	0.032	
Differential	Probiotic	30	6.07 ± 3.05	2.85 ± 2.10	-3.22 ± 2.95	0.006	0.012
Differential	Placebo	30	6.17 ± 3.00	5.25 ± 3.05	-.92 ± 1.80	0.041	
Quality of Life	Probiotic	30	5.10 ± 2.47	1.95 ± 1.40	-3.15 ± 2. 30	0.003	0.007
Quality of Life	Placebo	30	5.23 ± 2.06	4.05 ± 2.30	-1.18 ± 1.60	0.028	

Table 2: *ACSS domain scores at baseline and day 60.*

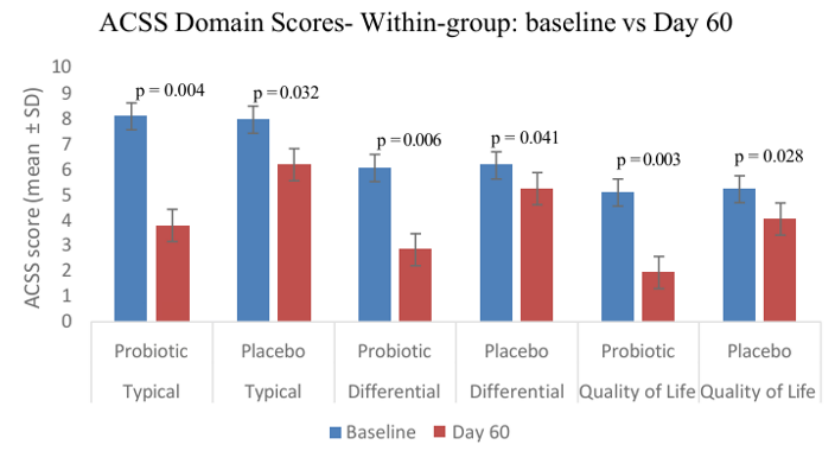

Figure 3: *Bar graph showing mean ACSS domain scores within each group for the test and placebo groups measured at baseline and at the end of treatment (EOT). Data are presented as mean ± standard deviation (SD). Baseline values are shown in blue, and EOT values are shown in red.*

The typical domain decreased from 8.10 ± 3.10 to 3.80 ± 2.45 in the *A. muciniphila* VHAKM group, corresponding to a mean change of −4.30 ± 3.15 (Table 2; figure 3). In the placebo group, the score decreased from 7.97 ± 2.76 to 6.20 ± 3.30, corresponding to a change of −1.77 ± 2.10 (Table 2; figure 3). The difference in change between groups was significant (p = 0.009). Similarly, the Differential domain decreased from 6.07 ± 3.05 to 2.85 ± 2.10 with *A. muciniphila* VHAKM (change, −3.22 ± 2.95), compared with a decrease from 6.17 ± 3.00 to 5.25 ± 3.05 with placebo (change, −0.92 ± 1.80; between-group p = 0.012, table 2; figure 3).

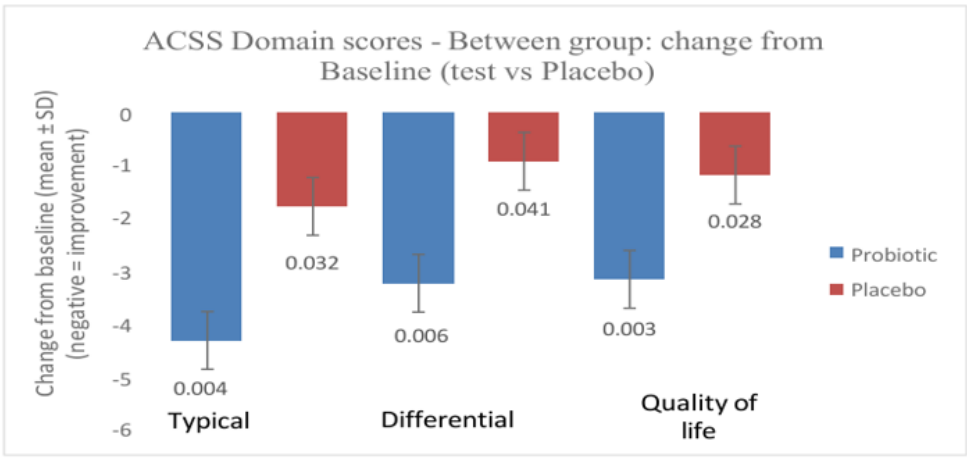

Figure 4: *Bar graph showing mean ACSS domain between groups for the test and placebo groups measured at baseline and at the end of treatment (EOT). Data are presented as mean ± standard deviation (SD). Baseline values are shown in blue, and EOT values are shown in red.*

Quality-of-Life scores decreased from 5.10 ± 2.47 to 1.95 ± 1.40 in the *A. muciniphila* VHAKM group (change,

−3.15 ± 2.30) and from 5.23 ± 2.06 to 4.05 ± 2.30 in the placebo group (change, −1.18 ± 1.60; between-group p = 0.007, table 2; figure 3). Thus, although a significant within-group improvement was observed in both treatment arms, the improvement across all three ACSS domains was significantly greater with *A. muciniphila* VHAKM than with placebo.

The mean change from baseline to Day 60 in all three ACSS domains was significantly greater in the *A. muciniphila* VHAKM group than in the placebo group (Table 2; Figure 4). Improvements were observed in the Typical (−4.30 ± 3.15 vs. −1.77 ± 2.10; p = 0.009), Differential (−3.22 ± 2.95 vs. −0.92 ± 1.80; p = 0.012), and Quality-of-Life domains (−3.15 ± 2.30 vs. −1.18 ± 1.60; p = 0.007).

Vaginal microbiota

Vaginal microbiota were assessed by qRT-PCR at baseline and following 60 days of intervention. At the end of treatment, lower levels of several potential uropathogens were reported in the *A. muciniphila* VHAKM group relative to placebo. Post-treatment values for *E. coli* were 2.70 ± 2.1 in the probiotic group compared with 4.68 ± 1.4 in the placebo group (p = 0.014) (Table 3; figure 5). Corresponding values were 1.52 ± 1.2 versus 2.67 ± 1.8 for *K. pneumoniae* (p = 0.0053) and 1.12 ± 0.96 versus 3.07 ± 2.6 for *P. mirabilis* (p = 0.0497) (Table 3; figure 5). The p-value for *K. pneumoniae* before treatment was significant (p = 0.014, table 3). Therefore, the post-treatment between-group comparison for *K. pneumoniae* should be interpreted with caution, and the observed reduction cannot be attributed to *A. muciniphila* VHAKM treatment. Confirmation using analyses that account for baseline differences would strengthen interpretation of this finding.

Conversely, bacteria generally associated with a favorable vaginal microbial environment were more abundant following *A. muciniphila* VHAKM supplementation. Post-treatment *Bifidobacterium* values were 4.73 ± 2.6 in the intervention group compared with 1.94 ± 2.8 in the placebo group (p = 0.018), while *Lactobacillus* values were 1.91 ± 0.8 and 1.12 ± 0.6, respectively (p = 0.007) (Table 3). There was a significant difference in *Lactobacillus* bacteria on baseline (p=0.046, table 3), therefore, the higher post-treatment *Lactobacillus* levels observed in the intervention group should be interpreted cautiously, as pre-existing differences between groups may have contributed to the observed outcome. Consequently, the change in vaginal *Lactobacillus,* just like for *K. pneumoniae,* cannot be attributed to the *A. muciniphila* VHAKM effect solely. These findings suggest that the intervention was associated with differences in vaginal microbial composition after 60 days, characterized by lower measured levels of selected uropathogens and higher levels of and *Bifidobacterium*.

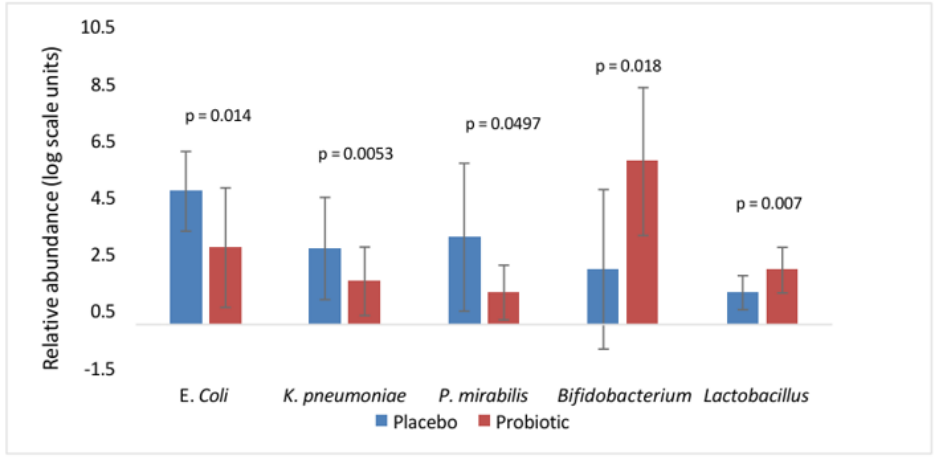

Figure 5: *Vaginal microbiota composition at day 60 (post-treatment), probiotic vs. placebo.*

Bacteria	Treatment group	Placebo	Probiotic	P-value between groups
E. coli	Baseline	3.37 ± 1.3	4.31 ± 2.5	0.075
	Post treatment	4.68 ±1.4	2.70 ± 2.1	0.014
K. pneumoniae	Baseline	2.10 ± 1.1	3.25 ± 2.2	0.014
	Post treatment	2.67 ± 1.8	1.52 ± 1.2	0.0053
P.mirabilis	Baseline	2.96 ± 1.6	3.05 ± 1.8	0.839
	Post treatment	3.07 ± 2.6	1.12 ± .96	0.0497
Bifidobacterium	Baseline	1.67 ± 1.6	2.52 ± 3.2	0.200
	Post treatment	1.94 ± 2.8	4.73 ± 2.6	0.018
Lactobacillus	Baseline	0.68 ± 0.5	1.24 ± 1.4	0.046
	Post treatment	1.12 ± 0.6	1.91 ± 0.8	0.007

Table 3: *Microbiota colonization from qRT-PCR.*

Vaginal pH and reproductive parameters

Vaginal pH decreased during treatment with *A. muciniphila* VHAKM from approximately 5.99 ± 0.73 at baseline to 4.90 ± 0.46 at the end of treatment. In comparison, vaginal pH changed only modestly in the placebo group, from 5.88 ± 0.83 to 5.74 ± 0.69 (Table 4). No substantial changes attributable to treatment were observed in the measured hormonal or reproductive parameters. FSH, LH, serum estradiol, and serum testosterone remained generally stable, and no significant between-group differences were reported (Table 4). Antral follicle count was also stable, changing from 8.80 ± 5.80 to 8.80 ± 5.40 in the intervention group and from 6.66 ± 5.85 to 6.71 ± 4.88 in the placebo group. Ovarian volume changed minimally, from 3.99 ± 0.47 to 3.95 ± 0.39 in the intervention group and from 3.88 ± 0.37 to 3.91 ± 0.37 in the placebo group (Table 4).

Safety and tolerability

A. muciniphila VHAKM was reported to be well tolerated during the 60-day intervention. No serious adverse events were reported, and no participants discontinued the study because of an adverse event. Hematological parameters showed only minor fluctuations and remained within clinically acceptable ranges. Similarly, changes in liver enzymes, renal-function markers, fasting blood glucose, and HbA1c were not considered clinically significant. Vital signs remained generally stable throughout the study. Taken together, these findings did not identify a clinically meaningful safety signal associated with *A. muciniphila* supplementation over the study period.

Characteristics	*A. muciniphila* VHAKM		Placebo	
	Baseline	End of visit	Baseline	End of visit
Vaginal PH	5.99 ± 0.73	4.90 ± 0.46	5.88 ± 0.83	5.74 ± 0.69
FSH (mIU/ml)	29.22 ± 22.85	29.34 ± 23.19	36.04 ± 30.53	35.02 ± 30.81
LH (mIU/ml)	24.23 ± 8.39	23.63 ± 8.45	26.21 ± 8.05	24.64 ± 8.50
Serum Estradiol Levels (pg/mL)	53.49 ± 23.11	52.35 ± 20.06	51.84 ± 24.54	49.73 ± 18.79
Serum Testosterone Levels (ng/mL)	12.79 ± 16.73	11.39 ± 15.58	26.10 ± 39.79	26.89 ± 43.25
Antral Follicle Count	8.80 ± 5.80	8.80 ± 5.40	6.66 ± 5.85	6.71 ± 4.88
Ovarian Volume	3.99 ± 0.47	3.99 ± 0.39	3.88 ± 0.37	3.91 ± 0.37

Table 4: *Vaginal pH and hormone levels results.*

Discussion

In this randomized, double-blind, placebo-controlled study, 60 days of oral supplementation with *Akkermansia muciniphila* VHAKM was associated with a lower reported incidence of symptomatic UTI in women with a history of recurrent infection. The intervention group also showed lower frequencies of culture-positive UTI, antibiotic use, and rescue-medication use, together with greater improvement across all three scored ACSS domains. These clinical observations were accompanied by changes in vaginal pH and microbial composition, while the measured safety, hormonal, and reproductive parameters remained generally stable.

The primary finding was the lower reported frequency of symptomatic UTI during treatment. The difference was observed not only in the reported mean number of episodes but also in the proportion of participants experiencing at least one UTI. Importantly, several supportive outcomes showed the same direction of effect. Culture-positive UTI and the need for antibiotic and rescue treatment were all less frequent in the *A. muciniphila* group. The agreement among these outcomes strengthens the clinical signal because the apparent treatment effect was not restricted to a single symptom-based measurement.

The ACSS results provide additional support for an effect on symptom burden. Both treatment groups improved over the 60-day period, emphasizing the importance of the randomized placebo-controlled design and demonstrating why within-group changes alone should not be interpreted as evidence of efficacy. Nevertheless, reductions in the Typical, Differential, and Quality-of-Life domains were consistently greater with *A. muciniphila* VHAKM. The between-group differences in change were significant for all three domains. These findings suggest that the intervention may affect not only UTI occurrence but also the severity and patient-perceived consequences of urogenital symptoms.

A potentially important observation was the concomitant alteration in vaginal microbial measures. Following treatment, the *A. muciniphila* VHAKM group exhibited lower measured levels of *E. coli*, *P. mirabilis* and higher levels of *Bifidobacterium* than the placebo group. The association between the vaginal microbiota and susceptibility to recurrent UTI is well established, particularly with respect to colonization by uropathogens and depletion of protective lactobacilli [13]. Previous probiotic approaches for recurrent UTI have consequently focused largely on restoring or maintaining *Lactobacillus*-dominated microbial communities [7,12].

The observed decrease in vaginal pH provides another potentially relevant finding. An acidic vaginal environment is generally associated with a lactobacilli-rich microbiota and may reduce the ability of several uropathogens to colonize the urogenital tract. *A. muciniphila* VHAKM supplementation was associated with a reduction in vaginal pH from approximately 6.0 to 4.9, whereas relatively little change occurred with placebo. Considered together with the microbiota results, this observation raises the possibility that modification of the urogenital microbial environment contributed to the clinical findings.

However, the present study does not establish the mechanism responsible for these changes. *A. muciniphila* is primarily recognized as a gastrointestinal microorganism, and the study did not demonstrate that orally administered *A. muciniphila* VHAKM colonized the vagina. Therefore, the increase in *Bifidobacterium* and decrease in selected uropathogens should not be interpreted as evidence of direct vaginal colonization by the administered organism. An indirect effect mediated through intestinal microbial ecology, microbial metabolites, host immunity, or gut-urogenital interactions is conceivable [10], but these mechanisms were not measured in the present trial and remain speculative. Mechanistic studies incorporating strain-specific detection, broader microbiome profiling, and relevant metabolomic or immunological endpoints would be required to determine how oral *A. muciniphila* VHAKM might influence the vaginal ecosystem.

The reduction in antibiotic use observed during the study may be particularly relevant in the context of recurrent UTI. Repeated antimicrobial treatment can contribute to antimicrobial resistance and may further perturb intestinal and vaginal microbial communities

[10]. A non-antibiotic intervention capable of reducing the frequency of symptomatic episodes could therefore have value beyond symptom reduction. Nevertheless, the current results should not be interpreted as supporting *A. muciniphila* VHAKM as a treatment for an established acute bacterial UTI or as a substitute for clinically indicated antimicrobial therapy. Rather, the findings concern its potential role as a preventive strategy in women predisposed to recurrent infection.

Safety is also important given the intended preventive use of probiotics. No serious adverse events or treatment-related discontinuations were reported, and clinically relevant abnormalities were not identified in hematological, hepatic, renal, metabolic, hormonal, or reproductive assessments during the intervention. The absence of meaningful changes in FSH, LH, estradiol, testosterone, antral follicle count, or ovarian volume additionally suggests that the observed changes in vaginal pH and microbiota were not accompanied by detectable alterations in the reproductive parameters evaluated. These results support short-term tolerability of the intervention, although the sample size and 60-day duration do not permit conclusions regarding uncommon adverse events or long-term safety.

Limitation of the Study

Several limitations should be considered when interpreting these findings. First, the study included only 60 participants, with 30 participants per treatment arm. The relatively small sample limits precision and the ability to detect uncommon safety outcomes, and was chosen based on feasibility considerations, including recruitment capacity, study duration, and available resources. Consequently, the study may have been underpowered for some endpoints, and the findings should be confirmed in larger adequately powered trials. Second, follow-up was restricted to 60 days. Recurrent UTI is inherently a longitudinal condition, and longer follow-up is necessary to determine whether any reduction in recurrence persists after supplementation and whether the effect remains evident over clinically relevant periods such as 6 or 12 months. Third, although qRT-PCR enabled targeted assessment of selected bacterial groups, this approach provides a narrower representation of microbial ecology than comprehensive sequencing-based microbiome analysis. The findings therefore demonstrate changes in the organisms specifically measured rather than global restructuring of the vaginal microbiome. Fourth, the study was conducted in women with a defined history of recurrent UTI, and the results should not automatically be generalized to other populations or to treatment of acute UTI, and lastly, multiple primary and secondary outcomes were evaluated without formal adjustment for multiplicity. Consequently, the possibility of inflated type l error cannot be excluded, and statistically significant findings for individual outcomes should be interpreted cautiously pending confirmation in larger studies with prespecified multiple comparison tests.

Within these limitations, the consistency across several independently assessed outcomes is noteworthy. The reported reduction in symptomatic UTI was accompanied by improvement in ACSS domains, lower antibiotic and rescue-medication use, lower abundance of selected uropathogens, increased *Bifidobacterium*, and a shift toward a more acidic vaginal pH. These findings provide a rationale for larger, independently replicated trials with longer follow-up. Future studies should additionally incorporate microbiome sequencing, strain-specific detection of the administered organism, standardized microbiological confirmation of UTI episodes, and prespecified analyses of antibiotic exposure to clarify both the magnitude and mechanism of any preventive effect.

Conclusion

In this randomized, double-blind, placebo-controlled study, 60 days of oral *Akkermansia muciniphila* VHAKM (1 billion CFU/capsule) supplementation was associated with a lower reported incidence of symptomatic UTI and greater improvement in urogenital symptom scores compared with placebo in women with recurrent UTI. The intervention was additionally associated with lower culture-positive UTI, antibiotic use, and rescue-medication use, as well as lower measured levels of selected vaginal uropathogens, increased Bifidobacterium, and a reduction in vaginal pH. No clinically meaningful effects on the evaluated hormonal or reproductive parameters were reported, and no serious adverse events or treatment-related discontinuations occurred. These findings suggest that *A. muciniphila* VHAKM warrants further investigation as a potential non-antibiotic strategy for prevention of recurrent UTI. Larger studies with longer

follow-up and comprehensive microbiome and mechanistic analyses are required to confirm the efficacy signal, establish its durability, and determine the biological mechanisms underlying the observed clinical and microbiological changes.

Conflict of Interest

This research was funded by Vidya Probiotics, India; an organization to which Prabhu Rajagopalan, Raksha Sunhare, and Shyamprasad Kodimule belong, and Subhendu Nayak belongs to Vidya USA.

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Data Availability

Data will be made available upon request.

Author Contributions

Prabhu Rajagopalan: Conceptualization, methodology, validation, investigation Raksha Sunhare: Investigation, writing - review and editing.

Shyamprasad Kodimule: Funding acquisition, supervision, writing - review and editing Subhendu Nayak: Project administration, supervision, writing - review and editing.

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