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# Probiotic and cranberry supplementation for preventing recurrent uncomplicated urinary tract infections in premenopausal women: a controlled pilot study

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**ABSTRACT**

**Objectives**: To assess efficacy and safety of Bio-Kult Pro-Cyan (BKPro-Cyan), a product containing two strains of Lactobacilli plus cranberry extract, for preventing recurrent UTIs in pre-menopausal adult women.
**Methods**: This was a randomized, double-blind, placebo-controlled pilot study. Subjects received BKPro-Cyan or placebo twice-daily for 26 weeks. The primary endpoint was the proportion of subjects with recurrent UTI at the end of the study.
**Results**: 115 subjects were screened; 90 were enrolled; 81 completed the study. After 26 weeks, a significantly lower number of women experienced recurrent UTIs with BKPro-Cyan compared to placebo (9.1 vs 33.3%; P = 0.0053). BKPro-Cyan produced statistically significant improvements compared to placebo for multiple secondary endpoints, including: greater number of subjects who experienced no UTIs (90 vs 67%; P < 0.05); longer time to first UTI (174 vs 90 days; P = 0.001); shorter duration of active UTI (5 vs 12 days; P = 0.009); Fewer subjects requiring antibiotics (3 vs 11; P < 0.05); and shorter median duration of antibiotic treatment (4 vs 7 days; P = 0.09).
**Conclusions**: BKPro-Cyan was safe and effective for preventing recurrent UTI in pre-menopausal adult women. These findings support the need for further well-designed trials to clarify the benefits that may be achieved.

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Bio-Kult Pro-Cyan; cranberry; microbiome; probiotics; urinary tract infection

## 1. Introduction

The role of the host-microbe ecosystem (microbiome) in health and disease is of growing scientific interest as evidenced by the National Institutes of Health (NIH) Human Microbiome Project [1], the Metagenomics of the Human Intestinal Tract (MetaHIT) consortium [2] and the United States' National Microbiome Initiative [3]. These initiatives recognize the complexity of the human microbiome in terms of composition, functions, dynamics, and interrelationships and its potential link to, and for treating/preventing, a range of diseases. Notably, microorganisms in the human gastrointestinal tract have been shown to influence physiological processes including immune function [4]. This has increased research aimed at developing novel microbiome-based treatment and prevention approaches. One intriguing possibility is the use of probiotics to improve the composition of the microbiota in favor of beneficial microorganisms. This approach has been tried in a number of infectious diseases, with the goal of limiting the activity of pathogenic bacteria [5].

Urinary tract infections (UTIs), the focus of our study, have been estimated to affect >50% of women at some stage in their lives [6], and between 25 and 30% of these individuals have at least one recurrence after the first infection [7]. As such, they represent a major clinical challenge in community practice, and they place a significant financial burden on healthcare systems [8]. The most common pathogens associated with UTIs belong to the Enterobacteriaceae family (*Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis*, Citrobacter spp. and Enterobacter spp.) [8]. Uropathogenic *E. coli* (UPEC) are a heterogeneous group of extra-intestinal *E. coli* that originate in the rectal microbiota and they account for approximately 80% of uncomplicated UTIs, and 95% of community-acquired UTIs [8–10]. The current strategy for managing UTIs is based on a combination of lifestyle measures and antibacterial therapy [7,8,11]. In women with recurrent UTIs, continuous prophylaxis with low-dose antibacterial regimens has been recommended [12]. However, the routine use of low-dose, daily antibiotics is now being questioned because of the widespread emergence of antibiotic-resistant strains [7,8,11]. In particular, antimicrobial resistance in uropathogenic *E. coli* is a concern [13,14] and the availability of alternative treatments is important. Furthermore, antibacterial drugs have been linked to gut and vaginal dysbiosis which is also a potential cause of recurrent infections [15].

A recent novel approach is the use of natural products, such as probiotics and cranberry supplements, that act on the microbiome to reduce colonization by uropathogens. The basis for this strategy is the strong link between vaginal health and UTIs, and the finding that pathogenic bacteria colonizing the female urinary tract are associated with ascending colonization from the fecal flora [7]. Indeed, the link between the microbiome and urological health and disease is of increasing clinical interest

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and has given rise to the concept of the female urinary microbiota [16,17]. This mode of therapy also avoids the complication of dysbiosis frequently seen with broad-spectrum antibacterial treatment [15].

Studies have shown that women with no history of UTIs had a Lactobacilli-dominant vaginal microbiota with the most common strains being *Lactobacillus crispatus, Lactobacillus jensenii*, and *Lactobacillus iners*, whilst patients suffering from recurrent UTIs were comparatively depleted of Lactobacilli [9,18]. Based on these findings it has been suggested that commensal *Lactobacillus* spp. may help protect the vagina from invading uropathogens [8,9]. This is the theory behind the administration of Lactobacilli-based probiotics to help maintain and restore a healthy microbiota effective in inhibiting colonization by uropathogens [8,9,19–21]. However, despite the promising potential of probiotics to prevent UTIs in the community, most randomized controlled trials up to 2015, as reviewed by the Cochrane group, failed to identify any significant clinical benefit [22].

Likewise, in a Cochrane review in 2012 involving 24 trials and >4000 patients, cranberry supplementation did not have a statistically significant benefit in preventing symptomatic UTIs [23]. Products such as tablets or capsules were also ineffective, although they had the same effect as taking antibiotics [23]. In two meta-analyses, both published in 2017, cranberry products were shown to reduce the risk of UTI recurrence by 26% [24] and 33% [25]. A drawback of the studies involving tablets and capsules was that few reported how much active ingredient was administered. This is important since it has been shown that at least 36 mg of cranberry proanthocyanidin (PAC) equivalents/d, divided into two doses (morning and evening), is needed to impart the anti-adhesion bioactivity thought to be necessary to prevent bacterial adhesion to uroepithelial cells lining the bladder wall [23,26]. The authors noted that more studies of tablets and capsules may be justified, but only if the recommended amount of PAC (at least 36 mg/d) is administered [23].

Based on these findings we investigated the efficacy and safety of Bio-Kult Pro-Cyan (BKPro-Cyan), a commercially available product containing probiotic strains (*Lactobacillus acidophilus* PXN 35, *Lactobacillus plantarum* PXN 47) and cranberry extract (36 mg/d PACs), for preventing recurrent uncomplicated UTIs in premenopausal adult women.

## 2. Methods

### 2.1. Study design

This was a randomized, double-blind, placebo-controlled, parallel-group pilot clinical trial performed in 4 centers across India between August 2016 and June 2018. The study was approved by an Institutional Review Board or Independent Ethics Committee at each study center. All participants were informed about the objectives, methodology and implications of the study, and those agreeing to participate were required to provide verbal and written consent prior to entry. The study was conducted in accordance with the ethical principles set out in the Declaration of Helsinki; Schedule Y of the Central Drugs Standard Control Organization, Ministry of Health and Family Welfare, Government of India; Ethical Guidelines for Biomedical Research on Human Participants, Indian Council of Medical Research (2006); and the International Conference on Harmonization, E6 – Guideline for Good Clinical Practice.

### 2.2. Patients

Female subjects aged 18 to 55 years who had suffered ≥2 episodes of uncomplicated acute UTI in the last 6 months, or ≥3 episodes of uncomplicated acute UTI in the last 12 months. Each individual needed to be available for the study duration, comply with the final protocol, and to avoid using any supplements/foods containing cranberries or probiotic supplements for the duration of the study. Finally, each participant was required to be incapable of becoming pregnant or, if of child-bearing age, to have a negative pregnancy test during screening and to use an approved contraceptive throughout the study (pregnancy tests were performed at all follow-up visits).

Exclusion criteria: active UTI; use of any antibiotic within 2 weeks of screening; known allergy to any ingredient in the treatments being administered; use of any natural product one month prior to starting the study; a positive pregnancy test; post-menopausal; concurrent use of corticosteroids, anticoagulants, antidepressants, other mood-stabilizing medications, or any medication that could interact with the supplement; significant concurrent illness or conditions including, psychiatric, cardiac (including poorly-controlled hypertension), renal (including anatomical irregularities, catheterization, renal stones or renal transplant); hepatic (including hepatitis B or C), neurological, endocrine, metabolic (including diabetes), or lymphatic disease that, in the opinion of the investigator, could adversely affect the subject's participation in the study; immunosuppressive disease (including HIV); and active participation in any clinical trial within one month of study entry.

### 2.3. Procedures

Following a screening visit (up to 2 weeks prior to treatment), patients fulfilling the inclusion criteria in the absence of any of the exclusion criteria, and who provided a written informed consent form, were included in the study and comprised the randomization group (Figure 1). All participants were advised to maintain their usual dietary practices throughout the study. Randomization into two groups was performed by an independent statistician using unique three-digit subject identification numbers [based upon a single-digit study center number followed by a two-digit individual number]. Half received BKPro-Cyan (ADM Protexin, Somerset, UK), one capsule twice daily, and the other half received a matching placebo (cellulose + coloring agent) one capsule twice daily.

BKPro-Cyan is a capsule formulation containing: cranberry extract (Vaccinium macrocarpon); probiotics (*Lactobacillus acidophilus* PXN 35, *Lactobacillus plantarum* PXN 47); and vitamin A (retinyl acetate; 160 µg/capsule). Each capsule contains a minimum of 18mg cranberry PACs and >500 million live probiotic microorganisms (>5 x $10^8$ CFU/capsule). The rationale for including *Lactobacillus acidophilus* PXN 35 and *Lactobacillus plantarum* PXN 47 in BKPro-Cyan is based on published literature showing significant inhibition of *E. coli* and *E. faecalis* by the two strains [27]. BKPro-Cyan capsules were administered with a meal and treatment was continued

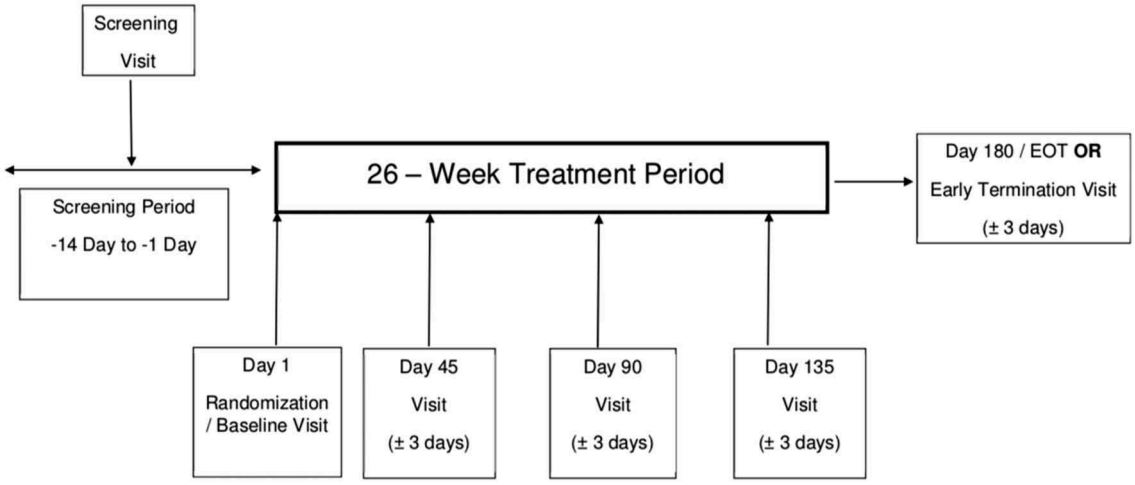


Figure 1. Study flowchart.

for a total of 26 weeks. An independent data-monitor (IDM) maintained treatment codes and allocation records, and these were locked until trial completion. However, a blinded interim analysis was performed by the IDM to ensure that all investigating centers were entering and uploading the information correctly onto the data entry system. Thus, the study was performed double-blind with all patients and clinical staff unaware of which treatment had been allocated.

A pre-study baseline screen was performed during which demographic data, medical history, vital signs, hematology, biochemistry, serology, urinalysis and urine culture were recorded. During treatment, patients returned to the clinic on days 45, 90, 135 and end-of-study (day 180 or discontinuation) when vital signs, urinalysis and pregnancy tests were checked and adherence to treatment and diary cards were evaluated. Urinalysis was performed by the investigators at the above-mentioned time points and during any unscheduled visits.

### 2.4. Efficacy assessments and endpoints

The aim of this pilot study was to determine whether BKPro-Cyan, a commercially available probiotic and cranberry-based natural supplement, was more effective than placebo at reducing the incidence of recurrent UTI episodes in susceptible adult women. As per European Association of Urology (EAU) guidelines uncomplicated UTI was diagnosed by > $10^3$ cfu/mL of uropathogens in a mid-stream sample of urine in participants presenting with symptoms of uncomplicated cystitis (dysuria, urinary frequency, urgency, suprapubic pain, and hematuria) [6]. Absence of UTI was confirmed for all patients at screening with urinalysis and culture. Patient diary cards were used to record UTI symptoms (dysuria, urinary frequency, urgency, suprapubic pain, hematuria) on a daily basis throughout the study.

### 2.5. Efficacy analyses

The number and percentage of recurrent UTI episodes in the BKPro-Cyan and placebo groups in both the full analysis set (FAS: all randomized subjects who received at least one dose of study drug) and per-protocol population (PP: all subjects who were 80% compliant with treatment and had no major protocol violations) were determined. The primary endpoint was the proportion (%) of subjects with a recurrent UTI by the end of 26 weeks' treatment.

*Secondary endpoints*:

- The proportion of subjects with 0, 1, 2 or more UTIs
- Time to first UTI after randomization
- Number of UTIs
- Duration of active UTI
- Duration of antibiotic treatment
- Number of antibiotic courses during the treatment period
- Adverse events (AEs) in the two groups with a focus on gastrointestinal AEs

### 2.6. Safety analyses

Tolerability/safety was determined in the FAS and included recording all AEs in the two groups including intensity and likely causality throughout the study. AEs were classified by System Organ Class (SOC) and Preferred Term (PT). Treatment-emergent AEs (TEAEs) and serious AEs (SAEs) were considered to be those events which first occurred on or after the start date, or those which worsened (increased in severity) after the start of treatment.

Special attention was given to gastrointestinal AEs which were a secondary endpoint in the study. Subjects were requested to record gastrointestinal AEs in their diaries. In addition, vital signs and urinalyses were measured throughout the study and laboratory safety tests (hematology and biochemistry) at the start and end of treatment (or on early discontinuation).

### 2.7. Statistical analyses

As this was a pilot study, with a relatively small number of participants, the statistical comparisons should be considered exploratory. Descriptive statistics were used to compare findings in the two treatment groups, and these included counts and percentages for categorical data. Continuous data were summarized using mean, standard deviation (SD), median, and

range (minimum and maximum values). A conventional sample size calculation based upon power and level of significance was not performed. Based on the use of pre-screening approaches to reduce screen fails, the plan was to screen 100 women with the goal of including 90 in the randomization process (45 subjects/group) and 80 (40 subjects/group) in the final analysis. This allows for a 10% withdrawal rate.

For the primary endpoint, the proportion (%) of subjects with a UTI recurrence by the end of 26 weeks' treatment, the Chi-square test was used. Due to limited experience with BKPro-Cyan, the assumed difference between the two groups (30% vs 10%) was selected empirically. For statistical comparisons, an α level of 0.05 was considered statistically significant.

For the secondary endpoints in the FAS population, time to first UTI recurrence (measured using Kaplan-Meier plots), duration of active UTI episodes, duration of antibiotic treatment, and number of active antibiotic courses, continuous data (mean, median, minimum and maximum) were recorded. Statistical analysis was performed using Fisher's Exact Test.

Safety data were summarized using counts and percentages for AEs, medical history, physical examination results and categorical urinalysis results.

All statistical testing was performed using R Software (R Foundation).

## 3. Results

A total of 115 women were screened, 90 subjects were randomized to treatment and 81 (90%) completed the study (Table 1). The reasons for discontinuation were consent withdrawn/subject request (n = 5; no further details captured) and lost to follow-up (n = 4). No subjects experienced severe TEAEs leading to study discontinuation and no major protocol deviations were reported during the study. There was no difference in the history of UTIs in the 12 months prior to enrollment between the groups. Among enrolled patients, the majority had 2 UTI episodes in both the BKPro-Cyan [mean (SD); 2 (0.5)] and placebo [2 (0.4)] groups in the previous 6 months (p = 0.8596), and the total number of UTIs in the 12 months prior to enrollment ranged from 2 to 4 in both groups (p = 0.9004). A summary of subject demographics and baseline characteristics for the FAS population is provided in Table 2. There were no numerical differences in treatment groups with respect to mean age, height, and weight (statistical analysis not performed). The majority of randomized patients were either surgically sterile/of non-child-bearing potential (17/45 and 15/45 placebo and BKPro-Cyan recipients, respectively) or used double-barrier contraception (male condom in combination with either a cap, diaphragm or sponge with spermicide (21/45 and 26/45 placebo and BKPro-Cyan recipients, respectively); an intrauterine device was used by 3 placebo and 1 BKPro-Cyan recipients, respectively. Regarding the time from last UTI to the day of enrollment, there was no significant difference ($P$ = 0.8988) between the BKPro-Cyan [median (range); 67 (26–248) days] and placebo [64 (16–212) days] groups. The results in this section primarily focus on those for the FAS population; PP results were not significantly different.

Table 1. Subject disposition and analysis populations.

| Number of Subjects | BKPro-Cyan | Placebo | Total |
|---|---|---|---|
| Screened, n | | | 115 |
| Screen failure, n | | | 23 |
| Withdrawn before randomization, n | | | 2 |
| Randomized, n | 45 | 45 | 90 |
| Completed the study, n (%) | 40 (88.9) | 41 (91.1) | 81 (90.0) |
| Discontinued from the study, n (%) | 5 (11.1) | 4 (8.9) | 9 (10.0) |
| Consent withdrawn/subject request | 3 (6.7) | 2 (4.4) | 5 (5.6) |
| Lost to follow-up | 2 (4.4) | 2 (4.4) | 4 (4.4) |
| Analysis Population, n (%) | | | |
| FAS Population | 44 (97.8) | 45 (100.0) | 89 (98.9) |
| PP Population | 40 (88.9) | 41 (91.1) | 81 (90.0) |

Abbreviations: n, number of subjects in the given category; FAS, full analysis set; PP, per-protocol; BKPro-Cyan, Bio-kult Pro-Cyan

### 3.1. Primary efficacy evaluation: proportion of subjects with recurrent UTI episodes at the end of 26 weeks of treatment

Following 26 weeks' treatment, statistically significantly fewer women experienced recurrent UTI episodes in the BKPro-Cyan group compared with placebo (9.1% vs 33.3%; $P$ = 0.0053; Chi-square test) (Table 3).

### 3.2. Secondary efficacy evaluation

For all secondary endpoints, BKPro-Cyan produced better results compared to placebo (Table 4).

### 3.3. Proportion of subjects with 0, 1, 2, or more utis

A higher proportion of subjects did not experience any UTIs in the BKPro-Cyan group compared to the placebo group, at the end of 26 weeks of treatment (90.9 vs 66.7%). Of the subjects who experienced a UTI at the end of 26 weeks' treatment, the majority experienced one episode in both treatment groups although significantly fewer patients in the BKPro-Cyan group experienced such events ($P$ < 0.05) [Table 3].

### 3.4. Time to first UTI after randomization

The median time to first UTI after randomization was higher in the BKPro-Cyan group compared with the placebo group (174 vs. 90 days; $P$ = 0.001). After randomization, the first UTI was reported from as early as day 4 for placebo versus day 154 for BKPro-Cyan.

### 3.5. Duration of active UTI episodes

The mean (SD) duration of active UTI was lower in the BKPro-Cyan group compared with the placebo group (5 [0.8] vs 12.2 [6.5] days). The active UTI duration ranged between 4 to 6 days for BKPro-Cyan versus 4 to 30 days for placebo.

### 3.6. Duration of antibiotic treatment for acute UTI and the number of antibiotic courses

Fewer subjects required antibiotics for an acute UTI in the BKPro-Cyan group versus the placebo group (3 vs 11; $P$ < 0.05). The number of antibiotic courses was also less in the BKPro-Cyan group versus the placebo group (3 vs 14; $P$ = 0.27). The median (SD) duration of antibiotic therapy was less in the BKPro-Cyan group compared to the placebo group (4vs 7 days; P = 0.09).

Table 2. Demographics and baseline characteristics – FAS population.

| | BKPro-Cyan N = 44 | Placebo N = 45 |
|---|---|---|
| Ethnicity, n (%) | | |
| South Asian | 42 (95.5) | 42 (93.3) |
| Race, n (%) | | |
| Asian | 44 (100.0) | 45 (100.0) |
| Age (years) | | |
| Mean (SD) | 34.6 (9.6) | 34.8 (10.1) |
| Height (cm) | | |
| Mean (SD) | 155.3 (7.7) | 156.6 (8.5) |
| Weight (kg) | | |
| Mean (SD) | 57.5 (11.3) | 56.1 (10.2) |
| UTI history (median, mean (SD), [range]) | | |
| UTI episodes in 6 months prior to enrollment (n) | 2, 2 (0.51), [0–3] | 2, 2 (0.42), [1–4] |
| Total UTI episodes in 12 months prior to enrollment (n) | 3, 3 (0.60), [2–4] | 3, 3 (0.58), [2–4] |
| Time from last UTI to enrollment (days) | 67, 77 (45.8), [26–248] | 64, 73 (36.1), [16–212] |

Abbreviations: FAS, full analysis set; N = number of total subjects; n. = number of subjects in the given category; SD = standard deviation; BKPro-Cyan, Bio-kult Pro-Cyan

Table 3. Proportion of subjects with recurrent UTI episodes at the end of 26 weeks of treatment (primary endpoint).

| Population/Visit | BKPro-Cyan | Placebo | BKPro-Cyan vs Placebo (P-value) |
|---|---|---|---|
| FAS Population, Number of subjects | 44 | 45 | |
| Visit 6 (Wk26): n (%) [number of recurrent UTI episodes] | 4 (9.1) [4] | 15 (33.3) [19] | |
| Chi-Square Test | | | 0.0053 |
| PP Population, Number of subjects | 40 | 41 | |
| Visit 6 (Wk26): n (%) [number of recurrent UTI episodes] | 4 (10.0) [4] | 15 (36.6) [19] | |
| 95% CI | (0.70; 19.30) | (21.84; 51.33) | (9.16; 44.02) |
| Chi-Square Test | | | 0.0048 |

Abbreviations: FAS, full analysis set; n, number of subjects with a recurrent UTI; BKPro-Cyan, Bio-kult Pro-Cyan; PP, per-protocol; Wk, week

### 3.7. Urine culture results

As per inclusion criteria, all patients included in the trial had negative urine culture at the pre-study baseline screen. During the trial only patients in the placebo arm made unscheduled visits and positive urine cultures were recorded on 18 occasions. There were no unscheduled visits in the BKPro-Cyan arm during the trial. At the end-of-study visit, urine culture identified 4 positive cultures out of 40 patients in the BKPro-Cyan arm and 1 out of 41 in the placebo arm.

### 3.8. Adverse events

Overall, 3 (6.8%) subjects in the BKPro-Cyan group experienced TEAEs during the study [abdominal distention (n = 1) and diarrhea (n = 2)] compared with none in the placebo group (Table 5). No subjects experienced severe TEAEs or TEAEs leading to study discontinuation. All reported TEAEs were mild in severity, were considered related to the study drug, and resolved without corrective treatment.

## 4. Discussion

In this pilot study the proportion of participants in the BKPro-Cyan arm with recurrent UTI episodes during the course of 26 weeks' treatment (the primary outcome) was significantly lower vs placebo (9.1% vs 33.3%; $P = 0.005$). In addition, a range of secondary endpoints such as the proportion of subjects with 0, 1, 2 or more UTI episodes ($P < 0.05$), time to first UTI episode ($P = 0.001$), number of UTI episodes, duration of active UTI episodes, duration of antibiotic treatment for an acute UTI episode and number of antibiotic courses during the treatment period were markedly improved in the BKPro-Cyan group (some achieving statistical significance as indicated). Notably, the majority of women in both groups did not experience any UTI episodes during the study (90% for BKPro-Cyan and 66.7% for placebo). Overall, treatment with BKPro-Cyan for 26 weeks was safe and well-tolerated. If these findings are confirmed in clinical practice, they have the potential to provide a cost-effective strategy for managing women suffering with recurrent UTIs, as was shown in a decision-analysis model comparing the effectiveness, cost, and health-related quality-of-life outcomes associated with commonly used strategies for the management of recurrent UTIs [28].

The findings with BKPro-Cyan are notable when compared with the literature since they are the first to suggest clinical benefit of an oral preparation in premenopausal women suffering with recurrent UTIs. In the aforementioned Cochrane systematic review involving 9 studies and 735 participants, no significant clinical benefit for probiotics administered orally or intravaginally (pessary) for different periods to women or girls with recurrent UTIs was observed in the group overall [22]. Interestingly, one study which also used a Lactobacillus-based probiotic (but administered intravaginally), noted robust and prolonged re-colonization with *Lactobacillus crispatus* in women with recurrent UTI [29]. This was associated with a trend toward a reduction in the incidence of UTIs [the rate of culture-confirmed UTI was 15% in the probiotic group, as compared with 27% for placebo (relative risk, 0.5; 95% CI, 0.2–1.2)]. Whilst these findings align with the results of our pilot study, they are

Table 4. Secondary efficacy endpoints at the end of 26 weeks of treatment.

| Parameter | BKPro-Cyan | | Placebo |
|---|---|---|---|
| **Summary of UTI episodes at the end of 26 weeks of treatment** | | | |
| FAS Population, | N = 44 | | N = 45 |
| Number of episodes | | | |
| Visit 6 (Week26), n (%) **0** | 40 (90.9) | | 30 (66.7) |
| 1 | 4 (9.1) | | 11 (24.4) |
| **2** | 0 | | 4 (8.9) |
| PP population | 40 | | 41 |
| Visit 6 (Week26), n (%) **0** | 36 (90.0) | | 26 (63.4) |
| **1** | 4 (10.0) | | 11 (26.8) |
| **2** | 0 (0.0) | | 4 (9.8) |
| P-value (Fisher Exact test) for 0 and 1 UTI [95% CI] | | 0.0430 [−0.37; −0.02] | |
| P-value (Fisher Exact test) for 0 and 2 UTI [95% CI] | | 0.0380 [−0.25; −0.01] | |
| **Time (days) to first episode of UTI from randomization** | | | |
| FAS Population, N | 44 | | 45 |
| n | 4 | | 15 |
| Mean (SD) | 175.3 (20.7) | | 79.3 (53.9) |
| Median | 173.5 | | 90.0 |
| Min, Max | 154, 200 | | 4, 162 |
| PP Population, N | 40 | | 41 |
| n | 4 (10.0) | | 15 (36.6) |
| Median | 174 | | 90 |
| Min, Max | 154, 200 | | 4, 162 |
| P-value (Wilcoxon Rank Sum test) [95% CI] | | 0.0010 [37; 159] | |
| **Duration (days) of active UTI episode** | | | |
| FAS Population, N | 44 | | 45 |
| n | 4 | | 15 |
| Mean (SD) | 5 (0.8) | | 12.2 (6.5) |
| Median | 5 | | 11 |
| Min, Max | 4, 6 | | 4, 30 |
| P-value (Wilcoxon Rank Sum test) | | 0.0095 | |
| **Duration (days) of antibiotic treatment for an active UTI episode** | | | |
| PP Population, N | 40 | | 41 |
| Number of subjects with an active UTI episode and requiring antibiotic course | 3 | | 11 |
| P-value (Fisher Exact test) | | 0.0372 | |
| Number of antibiotic courses | 3 | | 14 |
| P-value (Wilcoxon Rank Sum test) | | 0.2721 | |
| Median duration of antibiotic course | 4 | | 7 |
| P-value (Wilcoxon Rank Sum test) | | 0.0971 | |
| Min, Max duration of antibiotic course | 4, 5 | | 3, 16 |

Abbreviations: FAS, full analysis set; Max, maximum; Min, minimum; N, number of subjects in given analysis population; n, number of subjects with UTI episode; PP, per-protocol; SD, standard deviation; BKPro-Cyan, Bio-kult Pro-Cyan

Table 5. Overview of treatment-emergent adverse events: FAS population.

| | BKPro-Cyan N = 44 | Placebo N = 45 |
|---|---|---|
| Subjects with: | n (%) | n (%) |
| TEAEs | 3 (6.8) | 0 |
| TEAEs related to study drug | 3 (6.8) | 0 |
| TEAEs leading to discontinuation | 0 | 0 |
| TESAEs | 0 | 0 |
| Number of deaths | 0 | 0 |

Abbreviations: FAS, full analysis set; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; N, number of subjects in analysis population; n, number of subjects with TEAE/TESAE; BKPro-Cyan, Bio-kult Pro-Cyan

not as substantial, and intravaginal administration also suffered from the drawback of a high incidence of AEs (56%) such as vaginal discharge/itching, and abdominal discomfort.

Our study has a number of limitations which should be acknowledged. Firstly, the small number of patients included in this pilot study precludes robust statistical examination and may not identify potential less common AEs. In addition, we did not investigate immunological biomarkers or undertake microbiological testing of the gastrointestinal system, vagina or urinary tract which prevents us from determining the ecological impact of treatments. The design of the current pilot study also did not allow an evaluation of whether the combination of components in BKPro-Cyan is better than each component alone. Evidence supports the successful use of either probiotics [29] or cranberries [25] in preventing recurrent UTIs. Formulation of the product used in this study started with a primary focus on bacterial strains tested for their ability to inhibit two key uropathogens (*E. coli* and *E. faecalis*) [27]. Although evidence is currently lacking, the hypothetical mechanism of action of these probiotic strains includes a positive influence on the gastrointestinal microbiota to suppress uropathogens such as *E. coli* and *E. faecalis*, and also to colonize the vagina, or protect the lactobacilli dominance of that environment, to inhibit colonization by uropathogens which might lead to ascending infection of the bladder via the urethra. If these mechanisms exist then the site of action is the gastrointestinal tract and the vagina. In contrast to this site of action, cranberry PACs inhibit *E. coli* adhesins (notably P-fimbriae) achieving an anti-adhesion effect in urine when consumed at a dose of 36 mg/day [26]. Thus, both the postulated mechanism and site of action of each component were considered to be unique, with the hypothesis being that, in combination, they would provide enhanced preventative efficacy than either ingredient alone.

Conducting this study as a four-arm trial including cranberry PACs alone, probiotics alone, PACs plus probiotics, and placebo, would have enabled us to ascertain whether the combination was more effective than the individual components; however, this was not the design chosen for the current study. Despite these limitations, the study did highlight a statistically significant benefit for BKPro-Cyan in reducing the recurrence of uncomplicated UTIs in premenopausal adult women.

In conclusion, this pilot study showed that BKPro-Cyan was safe and effective for preventing recurrent UTIs in premenopausal adult women. It is the first study of its type, suggesting clinical benefit with an oral probiotic and cranberry extract combination product in a disorder commonly treated in community practice. The potential for resource savings and reductions in antibiotic usage are important objectives and, if confirmed, will be a significant step forward.

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## Author contributions

Study conception and design: S Kapadia, P Koradia, Y Trivedi, G Chanchu, A Harper. Acquisition of data: S Kapadia, P Koradia, Y Trivedi. Analysis and interpretation of data: S Kapadia, G Chanchu, AH. Drafting of manuscript: S Kapadia, A Harper. Critical revision: S Kapadia, P Koradia, Y Trivedi, G Chanchu, A Harper. All the authors have read and approved the manuscript.

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## Declaration of interest

A Harper is an employee of ADM Protexin International Ltd. All other authors declare that confirm that they have no other relationship with ADM Protexin International Ltd whose involvement in the study included funding of the study, supply of Bio-Kult Pro-Cyan® probiotic and placebo capsules, review of the draft manuscript and financial support for medical writing. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

## CONSORT guidelines

This study was conducted in adherence to the CONSORT guidelines.

## Ethics approval and consent to participate

Ethical approval was obtained from the Institutional Review Board or Independent Ethics Committee of each study center. Informed consent to participate in the study was obtained from all participants after they were informed about the objectives, methodology, and purpose of the study in an easily understandable way, and those who agreed to participate were required to provide verbal and written consent prior to entry.

## Reviewer disclosures

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