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A randomized, triple-blind, placebo-controlled, parallel study of the efficacy of D-mannose for urinary tract infection symptoms in women

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Abstract

Background: Urinary tract infections (UTIs) are common infectious disorders affecting 50% of healthy women at least once during their lifetime. Antibiotic treatment for UTIs may increase the prevalence of antimicrobial resistance and side effects, highlighting the need for safe and efficacious alternatives. This study investigated the effect of acute supplementation with UClear, a D-mannose product, on UTI symptoms.

Materials and methods: Women with at least 2 uncomplicated UTI symptoms, as assessed using the UTI Symptom Assessment (UTISA) questionnaire and urine nitrite and leukocyte testing, were randomized to receive UClear or a placebo for 3 days. The study outcomes included changes in the UTI symptom severity and bother scores, complete resolution of UTI symptoms, urine culture data, quality of life assessed using the RAND 36-Item Short Form Survey questionnaire, and rescue medication use. Study outcomes were measured from baseline to days 2, 3, and 4.

Results: The total UTISA severity scores were not significantly different between the groups. Participants supplemented with UClear had lower total UTISA bother scores after 3 days than the placebo group ($p = 0.027$). On day 4, 43% of participants receiving UClear had complete resolution of "frequency of urination," based on the severity scores, compared with 20% of participants receiving the placebo ($p = 0.032$). A greater proportion of participants supplemented with UClear reported improvements in the severity and bother scores of "incomplete voiding" ($p \geq 0.020$) and "urgency of urination" ($p \geq 0.059$), compared with the placebo group. The proportion of participants in the UClear group with urinary microbial growth improved from 50% at baseline to 29% by day 4 ($p = 0.020$). UClear supplementation was safe and well tolerated.

Conclusions: After 3 days of UClear supplementation, urination-related UTI symptoms improved compared with those of the placebo group. These improvements corresponded with significant improvements in the degree of discomfort due to those symptoms. Further investigations in at-risk populations are warranted to understand the efficacy of UClear in resolving UTIs.

Keywords: D-mannose; Urinary tract infections; Women's health; Prophylactic treatment; Dietary supplement

1. Introduction

Urinary tract infections (UTIs) are among the most common infectious diseases, affecting more than 150 million people annually [1] and contributing to an annual cost of more than 1.5 billion dollars in the United States alone.[2] Additionally, UTIs can have negative consequences on the quality of life and well-being.[3,4] Uncomplicated UTIs may present with frequent, urgent, and painful urination, whereas more severe cases can cause kidney infections, leading to fever, flank pain, nausea, and vomiting.[5] Because of structural differences in urological anatomy,[6] a greater proportion of UTIs occur in females. An estimated 50%–60% of women experience a UTI in their lifetime,[7] and 11% experience a UTI at least once annually.[8]

The diagnosis of a UTI is often based on self-reported symptoms and is sometimes accompanied by a urine dipstick test, laboratory urinalysis, and/or urine culture. However, despite the varying degrees of UTI severity, antibiotics are often prescribed without confirming the presence of bacteria via a urine culture or determining antibiotic sensitivity.[9] Given the increasing concerns regarding antimicrobial resistance, safe and efficacious alternative treatment strategies are needed. Furthermore, the side effects associated with antibiotic use may cause discomfort and increase the risk of other infections.[10] The European Association of Urology guidelines recommend initiating treatment with nonantibiotic management options to prevent recurrent UTIs and limiting antibiotic use to complicated or unresolved cases.[11]

D-mannose, a bioactive monosaccharide normally present in human metabolism for glycosylation, has been widely used as a dietary supplement.[12] Prophylactic supplementation with D-mannose has been shown to reduce the risk of UTI and UTI recurrence over long periods.[13–15] In a rat model of UTI, D-mannose administration reduced bacterial growth after 1 day.[16] However, to date, no

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randomized placebo-controlled trial has investigated the role of D-mannose in improving symptoms associated with acute and uncomplicated UTIs. Therefore, the objective of this clinical trial was to investigate the efficacy and safety of D-mannose supplementation to resolve UTI symptoms in women with uncomplicated UTIs.

2. Materials and methods

2.1. Study design and ethics approvals

This was a randomized, triple-blind, placebo-controlled, parallel clinical trial conducted at KGK Science Inc. (London, Ontario, Canada) between May 2023 and June 2024. The study consisted of a 4-day study period and a follow-up telephone call on day 7 (Fig. 1). At the screening/baseline visit, volunteers meeting the eligibility criteria were randomized to receive UClear or a placebo for 3 days. In-clinic assessments were performed at screening/baseline and on days 2, 3, and 4; the follow-up occurred on day 7.

This study was reviewed by the Natural and Non-Prescription Health Product Directorate, Health Canada (Ottawa, Ontario, Canada), and Institutional Review Board Services (Advarra, Aurora, Ontario, Canada). Unconditional ethical approval was granted on March 15, 2023 (Pro00070254). This study was retrospectively registered at clinicaltrials.gov (NCT06719115) and followed the Consolidated Standards of Reporting Trials reporting guidelines. All participants provided written informed consent prior to the initiation of the study.

2.2. Study participants

Individuals who met all the inclusion criteria and none of the exclusion criteria were randomized into the study groups at screening/baseline. Briefly, participants were nonpregnant females, aged 18–75 years, who had at least 2 uncomplicated UTI symptoms, as assessed using the UTI Symptom Assessment (UTISA) questionnaire, and urine dipstick test result that was positive for nitrites and leukocytes. The participants agreed to maintain a consistent lifestyle for the duration of the trial, including dietary habits, physical activity patterns, and medications/supplements.

Individuals were excluded if they had any of the following: an allergy, sensitivity, or intolerance to the UClear, placebo, or rescue medication ingredients; clinical signs and symptoms of an upper UTI (e.g., costovertebral pain or tenderness, nausea, vomiting, or fever); anatomical or functional urinary tract abnormalities and/or a diagnosis of kidney or other urinary tract disease/condition; a history of or current urological cancer; use of an indwelling catheter or intermittent catheterization; were within 3 days of the end of their menstruation, menstruating, or anticipating menstruation during the study; unable to provide informed consent and/or were cognitively impaired; or any other condition or lifestyle factor that, in the opinion of the qualified investigator (QI), could adversely affect the participant's ability to complete the study or its measures or posed a significant risk to the participant.

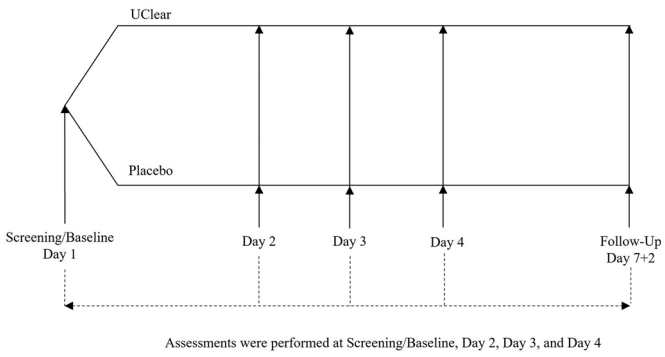

Figure 1. Study design.

2.3. Investigational products

The investigational product, UClear, contained 1.5 g of D-mannose and was manufactured by Inner Mongolia Ever Brilliance Biotechnology Co., Ltd. The placebo contained glucose and maltose. Participants were instructed to take 1 dose of their respective products twice daily for 3 days, with or without food, starting on day 1 (screening/baseline visit). The products were completely dissolved in a full glass of water, and the participants were instructed to ensure that any residue left in the glass was mixed with additional water and consumed. The first dose was administered in the presence of study personnel. If a dose was missed, participants were asked to take the missed dose as soon as they remembered but to not exceed 2 doses daily.

2.4. Randomization procedures

During screening/baseline, a blinded investigator assigned a randomization number to all eligible participants based on the study randomization list (www.randomization.com). The investigator was provided with a randomization schedule that indicated the order of randomization. Investigators, study personnel, statisticians, and participants were blinded to the study products.

The UClear and placebo were matched in appearance, to ensure allocation concealment. The products were packaged in sealed bottles identical in appearance and labeled according to the International Conference of Harmonization Good-Clinical Practice and applicable local regulatory guidelines. Unblinded personnel who were not involved in the study labeled the study products.

2.5. Compliance

To assess compliance with the study products, participants were asked to bring all unused and open packages to the study visit on day 4. The percent compliance was calculated by dividing the number of dosage units administered by the number of dosage units expected to be administered and then multiplying by 100. If there was a discrepancy between the amount of study product returned and the compliance information recorded in the study diary, the compliance was calculated based on the product returned, unless the participant provided an explanation for the loss.

2.6. Study outcomes

To investigate the efficacy of UClear in resolving UTI symptoms in women, the primary outcome was assessed as follows: 1) the difference in the proportion of participants with complete resolution of UTI symptoms on day 4 between the UClear and placebo groups and 2) the difference in changes from day 1 to day 4 in UTISA severity scores, including the frequency and urgency of urination, painful/burning urination, incomplete voiding, pelvic pain, low back pain, and hematuria, between the UClear and placebo groups. Secondary outcomes included the proportion of participants with complete resolution of UTI symptoms on days 2 and 3, symptom severity and bother scores assessed using the UTISA questionnaire, urine culture results, use of rescue medication, and quality of life assessed using the RAND 36-Item Short Form Survey (SF-36) questionnaire on days 2, 3, and 4. Safety outcomes

included postemergent adverse events (AEs) and clinically relevant changes in vital signs, clinical chemistry, and hematology.

2.7. Study procedures and assessments

At screening/baseline (day 1), the eligibility was assessed based on the medical history, current health status, inclusion and exclusion criteria, concomitant therapies, clinical chemistry, and hematology. A urine pregnancy test was conducted, and urine samples were collected for urine culture and dipstick tests for nitrates and leukocytes. Once eligibility was confirmed, the participants were randomized and administered the first dose of the study product. Participants were given their study products and diaries for the duration of the study. Daily study diaries were completed by the participants to record compliance with the study product and the consumption of water and other beverages, AEs, changes in health or concomitant therapies, and use of rescue medications.

The UTISA and RAND SF-36 questionnaires were administered on days 1, 2, 3, and 4. The UTISA questionnaire is a 14-item assessment of the severity and bother of 7 symptoms of uncomplicated UTIs.[17] Each item was scored on a 4-point Likert scale ranging from 0 to 3. Severity-related items were scored as 0 ("did not have"), 1 ("mild"), 2 ("moderate"), and 3 ("severe"). Bother-related items were scored as 0 ("not at all"), 1 ("a little"), 2 ("moderately"), and 3 ("a lot"). The complete resolution of symptoms was defined as 0 points for all the UTISA questionnaire components.[18] The RAND SF-36 questionnaire assesses the health-related quality of life over the past 4 weeks; however, to account for the acute infection timeline of an uncomplicated UTI, a modified recall period of 24 h was used, as demonstrated by Ellis and Verma.[19] The SF-36 measured the following 8 aspects: physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. The scores ranged from 0 to 100, with higher scores indicating a better state of health.

2.8. Urine analysis

Urine samples were collected for culture and sensitivity testing on days 1, 2, 3, and 4. Participants collected approximately 40 mL of midstream clean catch urine, and samples were stored at 2°C–8°C until analysis. Urine leukocytes and nitrites were analyzed on day 1 using Urinalysis Reagent Strips (Easy@Home Areta 10 Parameter (10SG) Urinalysis Reagent Test Strips).

2.9. Safety

Participants recorded AEs in their study diary, which were classified according to their duration, intensity (mild, moderate, or severe), frequency, and outcome. The QI determined the causal relationship of the investigational product to the AE as either "not related," "unlikely," "possible," "probable," or "most probable."

Hematology parameters included white blood cell counts with differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red blood cell (RBC) counts, hemoglobin levels, hematocrit levels, platelet counts, immature granulocyte counts, nucleated RBC counts, and RBC indices (mean corpuscular hemoglobin level and concentration, mean corpuscular volume, and red cell distribution width). Clinical chemistry parameters included aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, creatinine, and electrolyte (sodium, potassium, and chloride) levels; estimated glomerular filtration rate; and glucose level. All laboratory safety parameters were analyzed by LifeLabs (London, Ontario, Canada) using standardized procedures. The QI assessed the clinical significance of abnormal clinical chemistry and hematological parameters.

2.10. Statistical analysis

The sample size was calculated according to the methods of Cohen.[20] The independent Student's t test was used to calculate a sample size of 30 participants, with 15 randomized to each study group. A sample size of 30 participants had an 80% power to detect an effect size >1.1, with a 2-sided significance level of 0.05 and a 20% attrition rate.

The results represented the per protocol population, defined as the participants who consumed at least 80% of the investigational product or placebo doses, did not have any protocol deviations that affected the primary outcomes, and completed all study visits and procedures connected with the measurement of the primary variable. Continuous outcomes were analyzed using linear mixed models. The fixed effects were the group, visit, and their interaction, and the random effect was the participant ID. Residuals versus fitted value and quantile-quantile plots were generated to evaluate the model adequacy. Categorical outcomes were assessed using Fisher's exact test.

Continuous outcomes are summarized as means and standard deviations, and categorical outcomes are presented as frequencies and percentages. A p value ≤ 0.05 was considered statistically significant. Statistical analyses were performed using R (version 4.2.1).

3. Results

3.1. Study population

Of the 64 women who were screened and consented to participate, 30 were enrolled in the study (Fig. 2). The enrolled participants were predominantly European Caucasians (41.4%) between the ages of 19 and 65 years (Table 1). The demographics and lifestyle (alcohol or tobacco use and physical activity) were not significantly different between the groups. One participant was excluded from the per protocol population because of antibiotic use during the study period. At the screening/baseline visit, the participant presented with fever, cold sweats, sharp abdominal pain, and tightness in the lower abdominal area, for which a 7-day antibiotic treatment was prescribed on day 2 of the study period.

3.2. Proportion of participants with complete resolution of UTI symptoms

All enrolled participants had UTI symptoms on day 2 of supplementation. No significant differences in the proportion of participants with complete resolution of all UTI symptoms during and after supplementation were observed between the UClear and placebo groups. On days 3 and 4, 14.3% and 21.4% of participants supplemented with UClear, respectively, had complete resolution of UTI symptoms, compared with 0% and 13.3% of participants in the placebo group (p = 0.224). Of the individual UTI symptoms, a greater proportion of participants supplemented with UClear reported complete resolution of "frequency of urination" on day 4 compared with those in the placebo group (43% vs. 20%, p = 0.032). Furthermore, a greater, albeit nonsignificant, proportion of participants in the UClear group reported complete resolution of the "urgency of urination" severity on day 4, compared with those in the placebo group (43% vs. 20%, p = 0.353).

3.3. Total UTI symptom severity and bother scores

The total severity scores of the UClear and placebo groups significantly improved from baseline on days 2, 3, and 4 (p < 0.001) (Table 2). The total UTI bother score in the UClear group (2.36 ± 2.76) was significantly lower than that in the placebo group (4.80 ± 3.43) on day 4 (p = 0.027), while the total bother scores

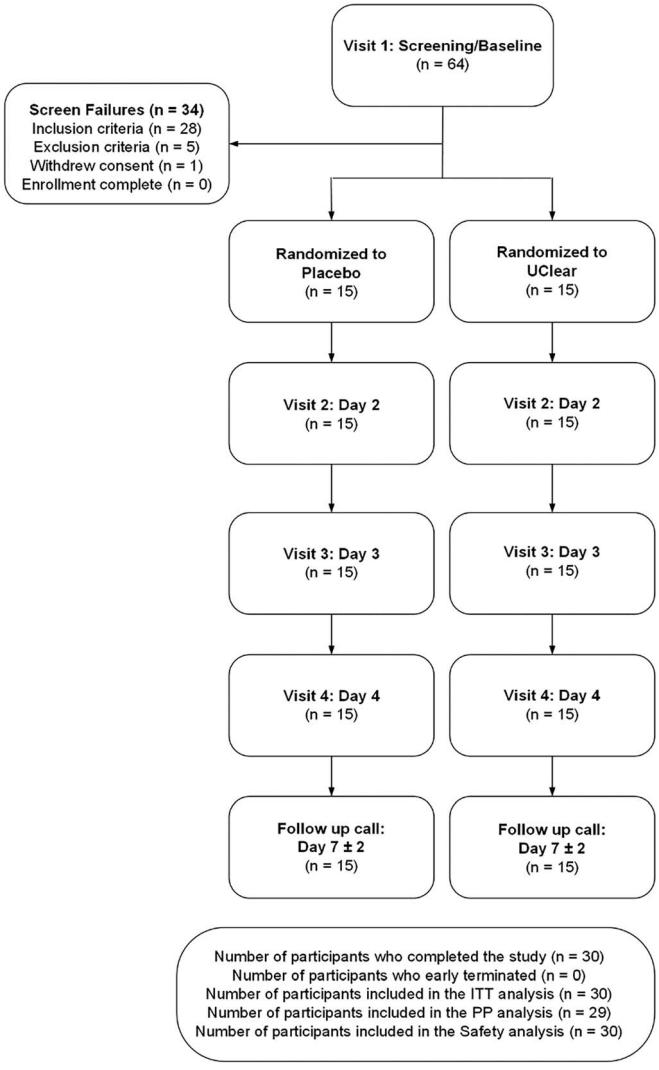

Figure 2. Flowchart of study participants.

significantly improved from baseline on days 2, 3, and 4 for both groups (Table 2). No other significant differences were observed between the UClear and placebo groups.

3.4. Individual UTI symptom severity and bother scores

The UTI symptom results are presented as changes from baseline to day 4. The changes in UTISA symptom severity and bother scores from baseline to days 2 and 3 for UTI symptoms are presented in Supplementary Tables 1 and 2, http://links.lww.com/CURRUROL/A76.

Frequency of urination At baseline, all participants in the UClear and placebo groups reported that "frequency of urination" severity was moderate-to-severe (Fig. 3A) and 93% and 87% of those in UClear and placebo groups, respectively, reported that "frequency of urination" bother was moderate-to-severe (Fig. 3B). On day 4, the distribution of the severity and bother scores of "frequency of urination" were significantly different between the 2 groups, with a greater proportion of participants in the UClear group reporting absent or mild symptoms and higher levels of bother compared with those in the placebo group (93% vs. 60%, $p = 0.032$) (Fig. 3).

Urgency of urination At baseline, 93% and 87% of participants in the UClear and placebo groups, respectively, reported that "urgency of urination" severity was moderate-to-severe (Fig. 4A) and 100% and 80% of those in the UClear and placebo groups, respectively, reported that "urgency of urination" bother was moderate-to-severe (Fig. 4B). On day 4, a greater proportion of participants supplemented with UClear than those receiving placebo showed improvements in both severity (43% vs. 20% with complete resolution, $p = 0.353$) and bother (64% vs. 27% with complete resolution, $p = 0.059$) scores (Fig. 4). From baseline to day 4, 93% of participants in the UClear group had improvements in the "urgency of urination" bother score, compared with 60% of participants in the placebo group ($p = 0.011$).

Incomplete voiding At baseline, moderate-to-severe 'incomplete voiding' was reported by 64% and 87% of participants in the UClear and placebo groups, respectively ($p = 0.452$) (Fig. 5A). After 1 day of supplementation, the distribution of "incomplete voiding" severity among participants was significantly different between groups, with a lower proportion of participants supplemented with UClear compared with those in the placebo group reporting moderate-to-severe severity (28% vs. 60%, $p = 0.048$). On day 4, the difference in "incomplete voiding" severity between groups approached statistical significance, with a greater proportion of participants reporting no symptoms in the UClear group compared with that in the placebo group (71% vs. 27%, $p = 0.073$) (Fig. 5A). Furthermore, the "incomplete voiding" bother score was significantly different between groups on days 3 (Supplementary Table 3) and 4 (Fig. 5B). On day 4, 28% of participants in the UClear group reported being bothered by "incomplete voiding," compared with 80% of participants in the placebo group ($p = 0.020$) (Fig. 5B).

Table 1

Demographic and general health information of the study participants.

Variable	Placebo (n = 15)	UClear (n = 14)	*p*
Age, yr, mean ± SD	48.00 ± 14.40	37.64 ± 13.09	0.052
Race, n (%)			
European Caucasian	8 (53.3)	4 (28.57)	0.333
South American	3 (20)	2 (14.29)	
Southeast Asian	1 (6.67)	4 (28.57)	
Central American	1 (6.67)	1 (7.14)	
Other	2 (13.33)	0 (0.00)	
East Asian	0 (0)	1 (7.14)	
South Asian	0 (0)	1 (7.14)	
Native or First Nations	0 (0)	1 (7.14)	
Regular alcohol consumption, n (%)			
Weekly, 3–6 times per week or more	1 (6.67)	0 (0)	0.907
Weekly, 1–2 times per week	2 (13.33)	4 (28.57)	
Monthly, 1–3 times per month	4 (26.67)	3 (21.43)	
Occasionally, a couple of times per year	1 (6.67)	1 (7.14)	
Not at all	7 (46.67)	6 (42.86)	
Use of tobacco products (including chewing tobacco, cigarettes, e-cigarettes, or vaporizers), n (%)			
Yes	3 (20)	1 (7.14)	
No	11 (73.33)	13 (92.86)	0.458
Former smoker	1 (6.67)	0 (0)	
Participation in regular exercise, n (%)			
Yes	9 (60)	7 (50)	
No	6 (40)	7 (50)	0.715

SD = standard deviation.

p Values for categorical variables were calculated using Fisher's exact test.

p Values for continuous variables were calculated using a *t* test.

Table 2

Changes in UTISA total symptom severity and bother scores from baseline to days 2, 3, and 4.

Time point	Placebo (n = 15)	UClear (n = 14)	*p*
Total UTISA symptom severity score			
Baseline (day 1), mean ± SD	10.67 ± 2.29	9.14 ± 2.14	0.139
Change from baseline to day 2, mean ± SD	−2.80 ± 2.24	−2.86 ± 3.16	0.958
p value from baseline to day 2	<0.001	<0.001	
Change from baseline to day 3, mean ± SD	−5.13 ± 2.67	−5.07 ± 2.97	0.955
p value from baseline to day 3	<0.001	<0.001	
Change from baseline to day 4, mean ± SD	−6.07 ± 3.83	−6.36 ± 3.89	0.789
p value from baseline to day 4	<0.001	<0.001	
Total UTISA bother score			
Baseline (day 1), mean ± SD	10.13 ± 2.70	9.43 ± 2.10	0.517
Change from baseline to day 2, mean ± SD	−2.60 ± 2.64	−3.43 ± 3.80	0.501
p value from baseline to day 2	0.003	<0.001	
Change from baseline to day 3, mean ± SD	−4.73 ± 3.33	−5.71 ± 3.81	0.426
p value from baseline to day 3	<0.001	<0.001	
Change from baseline to day 4, mean ± SD	−5.33 ± 4.13	−7.07 ± 3.69	0.160
p value from baseline to day 4	<0.001	<0.001	

SD = standard deviation; UTISA = Urinary Tract Infection Symptom Assessment.
p Values between and within groups were calculated using linear mixed models.

Other UTI symptoms At baseline, 43% and 50% of participants supplemented with UClear had moderate-to-severe symptom severity and bother, respectively, associated with "painful/burning urination." For those receiving the placebo, 73% and 67% of participants had moderate-to-severe severity and bother scores, respectively, associated with "painful/burning urination." Both groups had significant improvements in the severity and bother associated with "painful/burning urination" from baseline to day 4 ($p < 0.001$). Participants in the UClear and placebo groups reported improvements in "pelvic pain" severity and bother ($p \leq 0.026$) and "low back pain" severity ($p \leq 0.024$) from baseline to day 4. Two participants in the placebo group reported blood in their urine at baseline that was resolved by day 3 of supplementation.

3.5. Changes in urine cultures and use of rescue medication

At baseline, 50% of participants supplemented with UClear had microbial growth in their urine, compared with 21% of participants receiving placebo. On day 4, this proportion decreased to 29% in the UClear group and 13% in the placebo group. A significantly lower proportion of participants supplemented with UClear had a positive urine culture test on day 4 ($p = 0.020$), whereas those receiving the placebo had no significant differences. One participant from the UClear group reported using antibiotics for UTI treatment during the follow-up period. However, the proportion of participants using rescue medications was not significantly different during the supplementation or follow-up period (day 7).

3.6. Quality of life

Participants supplemented with UClear had significant improvements in several aspects of quality of life, including, "role limitations due to emotional problems," "emotional well-being," "social functioning," "bodily pain," and "general health," from baseline to day 4 ($p = 0.050$) (Table 3). Participants receiving the placebo had significant improvements in "physical functioning"

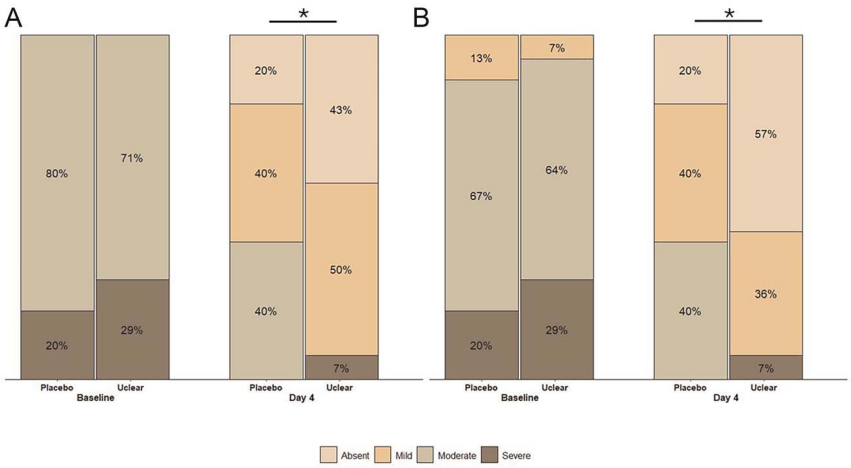

Figure 3. UTISA severity and bother scores of "frequency of urination" from baseline to day 4. Changes in the (A) symptom severity and (B) bother of participants. *Indicates a significant difference in the distribution of symptom severity or bother between the 2 groups. Data are presented as percentages. UTISA = Urinary Tract Infection Symptom Assessment.

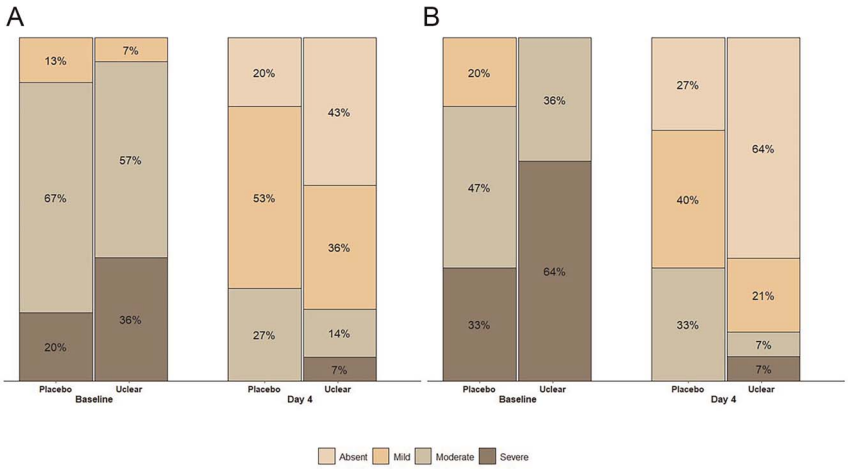

Figure 4. UTISA severity and bother scores of "urgency of urination" from baseline to day 4. Changes in the (A) symptom severity and (B) bother of participants. *Indicates a significant difference in the distribution of symptom severity or bother between the 2 groups. Data are presented as percentages. UTISA = Urinary Tract Infection Symptom Assessment.

($p = 0.020$), "social functioning" ($p = 0.012$), and "bodily pain" ($p = 0.035$) (Table 3).

3.7. Safety

Acute supplementation with UClear was safe and well tolerated by the study population. No clinically relevant changes in hematology, clinical chemistry, or vital signs were reported after 3 days of UClear supplementation, except for one instance of elevated bilirubin levels and one instance of elevated AST and ALT levels on day 4. Participants completed repeat laboratory testing in which bilirubin levels returned to normal, and AST and ALT levels were no longer clinically relevant, as assessed by the QI. Eleven postemergent AEs were reported by 8 participants: 5 in the UClear group and 3 in the placebo group. Two instances of abnormal laboratory findings and one instance each of fatigue, abdominal pain, abnormal menstruation, diarrhea, neck pain, and night sweats were reported in the UClear group, and 3 instances of headache were reported in the placebo group. All AEs were classified as "unlikely" or "not related" to the study product. Participants reported that they had recovered from all AEs by the end of the study period or at the follow-up.

4. Discussion

D-mannose is a simple monosaccharide that is not metabolized by humans, and most ingested D-mannose is excreted in urine.[21] Supplementation with D-mannose has previously been shown to reduce the risk of UTI and UTI recurrence over long periods.[13–15] To our knowledge, this is the first randomized, triple-blind, placebo-controlled study to examine the effect of the acute administration of D-mannose on the resolution of uncomplicated UTIs. This study demonstrated that oral supplementation with UClear, which provided 3 g of D-mannose, for 3 days was beneficial in improving UTI symptoms related to urination. Specifically, UClear supplementation resulted in a greater proportion of participants reporting the complete

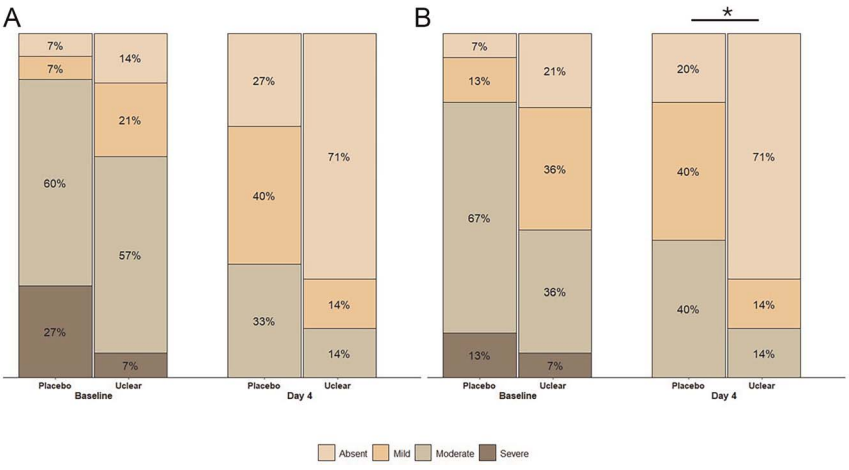

Figure 5. UTISA severity and bother scores of "incomplete voiding" from baseline to day 4. Changes in the (A) symptom severity and (B) bother of participants. *Indicates a significant difference in the distribution of symptom severity or bother between the 2 groups. Data are presented as percentages. UTISA = Urinary Tract Infection Symptom Assessment.

Table 3

Changes in the quality of life RAND SF-36 subscale scores from baseline to day 4.

Time point	Placebo (n = 15)	UClear (n = 14)	*p*
Physical functioning			
Baseline (day 1), mean ± SD	84.33 ± 17.10	92.50 ± 14.64	0.141
Change from baseline to day 4, mean ± SD	5.67 ± 14.25	3.93 ± 13.61	0.615
p value from baseline to day 4	0.020	0.117	
Role limitations due to physical health			
Baseline (day 1), mean ± SD	80.00 ± 35.61	82.14 ± 31.67	0.829
Change from baseline to day 4, mean ± SD	11.67 ± 48.06	14.29 ± 30.56	0.812
p value from baseline to day 4	0.129	0.074	
Role limitations due to emotional problems			
Baseline (day 1), mean ± SD	84.44 ± 35.34	73.81 ± 39.61	0.267
Change from baseline to day 4, mean ± SD	13.33 ± 37.37	26.19 ± 39.61	0.218
p value from baseline to day 4	0.067	0.001	
Energy/fatigue			
Baseline (day 1), mean ± SD	58.33 ± 19.70	57.50 ± 14.64	0.884
Change from baseline to day 4, mean ± SD	1.67 ± 16.65	6.79 ± 17.93	0.292
p value from baseline to day 4	0.621	0.054	
Emotional well-being			
Baseline (day 1), mean ± SD	76.80 ± 14.91	73.14 ± 12.30	0.457
Change from baseline to day 4, mean ± SD	4.00 ± 11.51	10.00 ± 14.53	0.129
p value from baseline to day 4	0.145	0.001	
Social functioning			
Baseline (day 1), mean ± SD	80.00 ± 26.64	76.79 ± 21.29	0.630
Change from baseline to day 4, mean ± SD	12.50 ± 25.44	16.07 ± 24.72	0.610
p value from baseline to day 4	0.012	0.002	
Bodily pain			
Baseline (day 1), mean ± SD	77.17 ± 19.13	73.57 ± 18.80	0.550
Change from baseline to day 4, mean ± SD	10.00 ± 24.03	15.18 ± 18.33	0.443
p value from baseline to day 4	0.035	0.002	
General health			
Baseline (day 1), mean ± SD	71.00 ± 18.05	64.29 ± 10.89	0.192
Change from baseline to day 4, mean ± SD	2.33 ± 15.34	5.36 ± 6.92	0.421
p value from baseline to day 4	0.372	0.050	
Health change			
Baseline (day 1), mean ± SD	58.33 ± 15.43	60.71 ± 18.90	0.724
Change from baseline to day 4, mean ± SD	0.00 ± 13.36	0.00 ± 0.00	1.000
p value from baseline to day 4	1.000	1.000	

SD = standard deviation.

p values between and within groups were calculated using linear mixed models.

resolution of frequency and urgency of urination compared with those who received placebo. This was further supported by a greater proportion of participants in the UClear group reporting improvements in symptoms and bother scores for the frequency and urgency of urination and incomplete voiding, compared with those in the placebo group. Hochstedler-Kramer et al.[22] investigated UTI symptoms and identified distinct profiles characterized by varying severities of specific UTI symptoms.[22] Specifically, they found that incomplete voiding and the urgency of urination commonly occur together, suggesting that UClear may have specific effects in resolving these UTI symptoms.

The population of this study consisted of 30 healthy women with at least 2 uncomplicated UTI symptoms and no clinical signs or symptoms of an upper UTI or kidney or other urinary tract disease or condition. The most commonly reported UTI symptoms include urination changes, such as the frequency, urgency, and associated pain [23]; these symptoms were observed in the population of this study, and frequent urination was reported as the most common symptom during previous UTI episodes. All participants in this study reported baseline frequency and urgency of urination during their UTI episode, whereas other symptoms, such as low back pain and hematuria, were less common. Although individuals with uncomplicated UTIs may report low back pain, this symptom is more commonly observed in severe or complicated UTIs.[24] Furthermore, frequent urination has been reported as rarely occurring with pelvic pain.[22] Taken together with the findings of the study population, the most prominent effect of UClear may be the resolution of common symptoms of uncomplicated UTIs, particularly the frequency and urgency of urination, which may be less severe compared with low back or pelvic pain.

In addition to self-reported symptoms, given the bacterial etiology of UTIs, bacterial growth in urine cultures was evaluated in this study. Despite a greater proportion of participants in the UClear group than in the placebo group having confirmed bacterial growth at baseline (50% vs. 21%), UClear supplementation resulted in a significant improvement in the distribution of bacterial growth, with only 29% of participants showing bacterial growth after 3 days. D-mannose has been proposed to prevent bacterial adhesion to urothelial cells,[25] which supports the observed improvements in UTI-related urination symptoms in this study. Among the various microorganisms that trigger UTIs, *Escherichia coli* is the most common pathogen responsible for both complicated and uncompleted UTIs.[26] D-mannose competitively inhibits bacterial adhesion to urothelial cells because its structure is similar

to the binding site of type 1 fimbriae, a virulence factor expressed on the bacterial cell wall. D-mannose prevents further bacterial colonization and translocation through the urothelium by blocking the virulence factor, which facilitates bacterial elimination through urination.[25,27]

UClear supplementation for 3 days during an acute UTI was safe and well tolerated in the study population. None of the reported AEs was related to the study product, and the participants reported recovery from all AEs by the end of the study period or upon subsequent follow-up. Notably, 93% of the participants did not require antibiotics for UTI treatment during the study or follow-up period. Previous randomized controlled trials investigating the effect of antibiotics in the treatment of uncomplicated UTIs demonstrated that 25%–50% of women with UTI symptoms recovered within a week without using antibiotics.[28,29] Therefore, the widespread use of antibiotics in the treatment regimen of all types of UTIs is concerning, given that individuals with recurrent UTIs are more likely to develop complications and side effects such as antibiotic resistance.[30] UClear supplementation is a promising intervention during the early stages of uncomplicated UTIs, as D-mannose may resolve symptoms and avoid the need for pharmaceutical interventions. Emerging evidence suggests that D-mannose plays a protective role in recurrent UTIs, with an efficacy similar to that of antibiotics in delaying UTI onset.[14,15,31] Moreover, a combination of antibiotics and D-mannose has been shown to be more efficacious in reducing UTI symptoms compared with antibiotics alone.[32,33] In fact, the use of a combination of antibiotics and nutraceuticals in individuals with antibiotic-resistant strains results in a significantly higher treatment success rate than the use of antibiotics alone.[32] Future studies investigating the effects of UClear, with or without antibiotics, in women with recurrent UTIs are warranted.

While most studies on uncomplicated UTI in women have evaluated the clinical management of UTI symptoms, the impact of UTIs on quality of life and emotional well-being is poorly understood.[34,35] A recent study reported that women experience feelings of helplessness and fear regarding treatment failure and recurrent UTIs.[3] In this study, improvements in UTI symptoms with UClear supplementation corresponded to significant improvements in various aspects of quality of life, including "role limitations due to emotional problems," "emotional well-being," "social functioning," "bodily pain," and "general health." While recurrent and single cases of UTI have similar clinical features and diagnostic testing, individuals with recurrent UTIs are more prone to a poor quality of life than those with nonrecurrent uncomplicated UTIs.[36] The administration of effective nonantimicrobial prophylactics for the prevention of recurrent UTIs has been shown to significantly improve quality of life.[37] In the current study, the acute administration of D-mannose showed beneficial effects in the resolution of UTI symptoms as well as the degree of bother, providing a rationale for investigating the efficacy of UClear in treating symptoms and improving the quality of life. Notably, aspects of quality of life were also improved in the placebo group over the study period. This improvement is likely due to the possible resolution of UTIs without pharmaceutical intervention, as mentioned above, and to the possible organic resolution of UTI symptoms in as little as 7 days, as shown in ≤50% of community-dwelling patients with UTIs.[38]

While this study provides evidence to support future research examining the role of D-mannose in the resolution of uncomplicated UTIs, the study had several limitations. This study examined the resolution of UTIs in females aged 18–75 years. UTIs are more prevalent in postmenopausal women,[39] and the use of antibiotics in the aging population can significantly impact the gut and urinary microbiome, with a long-term risk of recurrent UTIs.[40,41] Therefore, future studies should investigate the efficacy of UClear in reducing acute UTI symptoms and recurrent episodes in postmenopausal women. Furthermore, the study population was predominantly European Caucasians, which limits its generalizability to other races/ethnicities.

5. Conclusions

The results of this study demonstrated that a greater proportion of participants experienced improvements in UTI symptoms related to urination after 3 days of UClear supplementation compared with a population of women with acute uncomplicated UTIs who received a placebo. Improvements in the severity of UTI symptoms corresponded to significant improvements in the degree of bother associated with those symptoms in the UClear group. Furthermore, UClear supplementation improved aspects of quality of life related to bodily pain, general health, and social and emotional well-being, which can often negatively impact this population. Importantly, UClear supplementation was safe and well tolerated in the study population, providing a valuable alternative for the treatment and recovery from uncomplicated UTIs.

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Conflict of interest

EN, YZ, CZ, and XL are employees of KEB Nutraceuticals USA, Inc. RGS, HA, DCC, MM, NG, and EDL are employees of KGK Science, Inc, and have no competing interests to declare.

Author contributions

RGS, EDL, HA: Data interpretation, visualization, writing—original draft preparation, review, and editing;
DCC, NG: Study conduct supervision;
MM, DCC, EDL: Study design, writing—review and editing;
EDL, RGS, EN, YZ, CZ, XL: Study design, data interpretation, writing—original draft preparation, review and editing, supervision.

All authors read and approved the final manuscript. All named authors meet the International Committee of Medical Journal Editors criteria for the authorship of this article, take responsibility for the integrity of its research and content, and have approved the publication of this version.

Statement of ethics

This study was approved by the Natural and Non-Prescription Health Product Directorate, Health Canada, Ottawa, Ontario, and ethical approval was granted by the IRB Services, Aurora, Ontario (Pro00070254). The study was conducted in compliance with the ICH-GCP guidelines and in accordance with the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from all participants before the initiation of any study procedure. This study was retrospectively registered with ClinicalTrials.gov (NCT06719115).

Data availability

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

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