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Research Article

Prospective Study on the Efficacy and Safety of Uronext® in Parallel Groups in Women with Acute Cystitis

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Abstract

Uncomplicated lower urinary tract infections (LUTI) are one of the most common infections in adult women. LUTI are often relapsing and consequently significantly affect the quality of life of affected population. Antibiotics are treatment of choice in the case of LUTI occurrence, but especially due to the increasing pathogen resistance alternative approaches are being researched. We aimed to evaluate the efficacy and safety of the Qcran®, D-mannose and vitamin D3 based food supplement in women with acute cystitis and its effect on the recurrence of LUTI. We screened 111 female patients aged 18 - 80 years, with active acute cystitis, that was confirmed by a positive bacteriological urine test. Eligible participants were randomized into 2 parallel groups, in a 1:1 ratio, to receive either standard single dose of antibiotic therapy or antibiotic therapy and food supplement. After 12 weeks, proportion of patient without cystitis relapse in the group with scheduled supplementation was significantly higher than in control group. 77,6% versus 19,2% ($p < 0.0001$). By the end of the trial the difference in the mean recurrence of the disease was 0,78 ± 0,63 and reached statistical significance ($p < 0.0001$). According to ACSS QoL subscale and VAS QoL scale, quality of life significantly improved in the supplement group at all time points, as compared to control group.

Uronext® present a new, effective and well tolerated approach to improved management of LUTI in adult women.

Keywords: *Cystitis; Women; Cranberry; D-Mannose; Supplement; Antibiotic; Recurrence; Quality of Life*

Abbreviations

LUTI: Lower Urinary Tract Infections; *E. coli: Escherichia coli;* PAC: Proanthocyanidin; GCP: Good Clinical Practice; HIV: Human Immunodeficiency Virus; HbA1c: Hemoglobin A1c; VAS: Visual Analog Scale; QoL: Quality of Life; ACSS: Acute Cystitis Symptom Score Questionnaire; ECG: Electrocardiography; AEs: Adverse Events; SAEs: Serious Adverse Events; ICF: Informed Consent Form; ALT: Alanine Transaminase; AST: Aspartate Aminotransferase; CFU: Colony Forming Unit; PP: Per Protocol; BMI: Body Mass Index; SD: Standard Deviation; CI: Confidence Interval; V1: Visit 1; V2: Visit 2; n: Number; UTI: Urinary Tract Infection

Introduction

Uncomplicated lower urinary tract infections (LUTI) are characterized by a bacterial infection, usually occurring in healthy women who do not have concomitant chronic diseases and anatomical changes in the urinary tract. Risk factors include frequent sexual intercourse, previous LUTI, use of spermicides as a contraceptive, and a family history of LUTI [1]. Typical LUTI symptoms include frequent urination (pollakiuria), painful urination, urination in small portions (dysuria), urgency, blood in the urine (hematuria), and, if an infection develops in the upper urinary tract, fever and pain in the lumbar region on the affected side [1-3]. It is estimated that up to 50% of women experience at least one episode of LUTI in their lifetime [4] and that 20 - 30% of them have at least one re-current LUTI [5]. LUTI are associated with significant morbidity leading to limited activity and absenteeism [6].

Urinary tract infections often relapse with at least 2 reported episodes within 6 months (with fully treated bacterial infection using antibiotics between flare-ups) or 3 episodes within the past 12 months [1]. *Escherichia coli (E. coli)* is the most common uropathogen (80%) causing infection in the urinary tract, followed by *Staphylococcus saprophyticus* (10 - 15%). Other microorganisms such as *Enterococcus, Klebsiella, Enterobacter* and *Proteus* are found in significantly fewer patients [7-9]. The main infectious agents in patients with recurrent LUTI are *E. coli* and *Enterococcus faecalis* (formerly known as *Streptococcus faecalis*) [9]. In practical medicine, it is quite difficult to differentiate a relapse from an untreated episode of a previous infection, since sterile urine does not always mean an infectious agent has been dealt with successfully. Sometimes, small amounts of microbes below the testing limit are not documented in laboratories and reported to the clinician, although they may cause a recurrence of infection [10].

Recurrent LUTI can have a detrimental effect on women's health, their personal and social relationships, and their work performance. The results of a 6-month international observational study showed that recurrent LUTI had a negative im-pact on the quality of life of patients and that this could be improved via effective preventive measures [11].

Non-antibiotic preventive strategies against LUTI include behavioral therapy (urination before and/or after intercourse, wiping from front to back, etc.), diet modification, increased water intake [12], urine acidification using ascorbic acid (vitamin C) [13,14], cranberry as a food supplement [12], oral or vaginal probiotics [15-18], topical or oral estrogens [17], methenamine salts [12], and novel immunomodulatory agents [19]. However, the evidence base for many of these prevention strategies is weak or absent [12].

Thus, new effective nondrug solutions against LUTI are of undoubted interest for practical medicine, especially considering the increasing resistance of uropathogenic microorganisms to commonly used antibacterial agents [19]. Uronext® (UN) is a food supplement containing a combination of three active ingredients in a clinically relevant dosage, providing a complex synergistic effect to address LUTI. Qcran® is a 100% natural whole-fruit cranberry powder standardized to 36 mg of proanthocyanidins (PAC). Due to its content of PAC, Qcran® exhibits an anti-adhesive effect preventing *E. coli* from attaching to the bladder or urethra wall. In addition, it has antioxidant, anti-inflammatory, diuretic, and antimicrobial effects. Qcran® creates an unfavorable environment in the bladder and urinary tract, resulting in *E. coli* being unable to infect the mucosal surface and instead being flushed out of the urinary system [20,21]. D-mannose is a saccharide normally present in human metabolism, which acts mechanically against uropathogens, using mechanism similar to cranberry PAC. After oral intake it is absorbed in the intestine but not metabolized, travels to the urinary system unchanged and attaches to the *E. coli* cells, preventing their adhesion. As a result, *E. coli* is excreted in the urine without adversely affecting the urinary system [22-24]. Vitamin D3 contributes to the normal function of the immune system and healthy inflammatory response [25], promotes the synthesis of antimicrobial peptides that protect against uropathogens [26] and induces tight junction proteins in the urinary bladder, strengthening the epithelial barrier and, thus, improving the protection against LUTI [27].

Aim of the Study

The aim of this prospective study was to evaluate the efficacy and safety of the food supplement UN in women with acute cystitis and its effect on the recurrence of LUTI.

Materials and Methods

Study design

Study was designed as an open label, randomized, parallel study. It was carried out at Federal State Budgetary Educational Institution of Higher Education "A.I. Evdokimov Moscow State University of Medicine and Dentistry", Ministry of Health of the Russian Federation, on the basis of the S.I. Spasokukotsky Municipal Clinical Hospital between April 2021 and February 2022. Study was conducted in accordance with the ethical principles contained in the Declaration of Helsinki, which are consistent with good clinical practice (GCP) and applicable regulatory requirements of the Russian Ministry of Health. Study documentation was approved by Intercollegiate Ethics Committee, operating by Association of Medical and Pharmaceutical Universities. Study was registered at www.ClinicalTrials.gov #NCT05945667.

Study therapy

Participants were randomized into 2 comparative parallel groups, in a 1:1 ratio. Group assignment was based on random numbers generated using a validated computerized system. At baseline visit both groups received single dose of Monural® (Zambon Switzerland Ltd., Ltd.), while the second group additionally received food supplement Uronext® (Petrovax Pharm, Russia). Active ingredient in Monural® is fosfomycin trometamol 3g, antibiotic used to relieve LUTI exacerbations, that is considered standard therapy for the indication. UN is a food supplement, manufactured, developed, and supplied by PharmaLinea Ltd. (Ljubljana, Slovenia). UN contains 2000 mg of D-mannose, 500 mg of Qcran® and 40 IU of vitamin D3. Participants in the second group took the food supplement once a day for 7 days, every other week for 3 months. Monural® and UN were available in sachets, that were mixed with a glass of water and taken regardless of the meal.

Study population

The study included female patients aged 18 - 80 years, with active acute cystitis, that was confirmed by a positive bacteriological urine test. Participation in the study was not possible for individuals that had, at the time of inclusion, upper urinary tract infection, congenital malformations of the genitourinary organs, underwent surgical interventions on the genitourinary system or had any other disease of the genitourinary system, that requires specialized treatment. Participants with diabetes mellitus with poor glycemic control (HbA1c ≥ 8%), active hepatitis, uncontrolled human immunodeficiency virus (HIV) infection, or the presence or history of any malignant neoplasm were excluded from the trial.

We also excluded anybody with aggravated allergic history or hypersensitivity to any of the components included in the study products, anybody with the history of drug or alcohol addiction in the last 5 years, anybody currently pregnant, breastfeeding or planning pregnancy during the study period, or anybody participating in another clinical study in the last 6 months. Investigator could also decide to exclude any individual, with any clinical or other condition, including uncontrolled physical or mental conditions, that, in their opinion, might increase the risk of patient withdrawal from the study, prevent the patient from fulfilling study requirements or completing the study.

Considering the possible withdrawal of patients at the screening stage and after the randomization procedure, not less than 111 patients were screened.

Study outcomes

Primary outcome was defined as the proportion of patients who had no relapses of the disease by the visit 3. Each cystitis relapse was confirmed either by a urine culture count above 10^3 CFU/ml or if Monural® self-administration successfully relieved the symptoms.

Study protocol included several secondary outcomes. A recurrence rate from baseline to visit 3 was evaluated. 100 mm visual analog scale (VAS) was used for evaluation of pain intensity, severity of urge to urinate and urination frequency at baseline and after 6, 24, 48 and 72 hours. 0 on the scale indicated that the condition wasn't bothering, while 100 represented strongly bothering condition. Total scores and changes from the baseline levels were calculated for each symptom. Based on the Urination diary urination frequency and average urine volume were assessed on days 1, 2 and 3 and compared between the groups. The proportion of patients without notable microorganism growth during bacteriological urine analysis at visit 2 and 3 was analyzed. The change in parameters recorded by VAS quality of life (QoL) and acute cystitis symptom score questionnaire (ACSS) was calculated for visits 2 and 3 as compared to the baseline levels. Compliance to the therapy regimen was determined at visits 2 and 3.

Safety parameters included assessment of vital signs (blood pressure, heart rate, body temperature), instrumental assessment (ECG), concurrent therapy assessment and laboratory assessment (complete blood count and biochemical blood test, urine analysis). Throughout the study potential adverse events (AEs) and serious adverse events (SAEs) were recorded. Their frequency and frequency of early termination due to their occurrence were compared. Any AE was classified as mild, moderate, or severe, and the nature of their occurrence to the products in the study were determined.

Study procedures

Patients' recruitment was carried out in 1 stage. Participants were required to make 3 visits to the clinic. In case of exacerbations additional relapse visits were necessary. Visit 1 was the first day of the study and consisted of the screening procedures, randomization, and therapy launch.

Screening started with signing the written Informed Consent Form (ICF). Participants were assigned a five-digit screening number (XXYYY, where XX is the center number, YYY is the patient number). Numbers were assigned in ascending order as patients signed the ICF. All screened patients were entered into the Screening and Randomization Log. During the screening, the patient's compliance with the selection criteria for the study was confirmed: compliance with all inclusion criteria and the absence of all non-inclusion criteria.

Patient assessment included review of medical history, prior and current concomitant therapy, and number of UTI exacerbations over the past year. Demographic and anthropometric data were collected, physical examination with blood pressure, heart rate, respiratory rate and axillary temperature measurements were performed.

Laboratory analysis consisted of complete blood count analysis, biochemical blood tests for total protein, alkaline phosphatase, alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, glucose and cholesterol levels. If a patient haven't performed the following tests in the last 6 months, also serological blood test for HIV, syphilis, viral hepatitis B and C were necessary. Urinalysis with sediment microscopy was performed, together with antibiotic sensitivity test on the bacteria in the sample, if same tests haven't been done in the last 7 - 10 days. Women with preserved reproductive potential did a urine pregnancy test.

If necessary, according to the investigator, an ultrasound examination of the kidneys, bladder and pelvic organs was performed to exclude the presence of bladder stones and tumors, as well as to identify special forms of inflammatory lesions.

Participants received the urination diary, patient's diary and 100-mm VAS scale, with the instruction to complete it before receiving the therapy and after 6, 24, 48 and 72 hours. Baseline levels for the ACSS, and VAS QoL questionnaire were recorded.

Visit 2 was an outpatient visit at the end of the therapy course carried out on 8 ± 1 days after the study launch. Physical evaluation, concomitant therapy, laboratory analyses of clinical and biochemical parameters, urinanalysis, and bacteriological examination were performed in the same scope as at visit 1. Compliance with exclusion criteria was assessed and potential withdrawn patients were to be

replaced. New entries were made for 100 mm VAS scale, VAS QoL and ACSS and compared against the baseline values. Entries in Urinary Diary and Patient's Diary were reviewed, and all adverse events were registered. Patients returned remaining drugs or food supplements, compliance to therapy was determined.

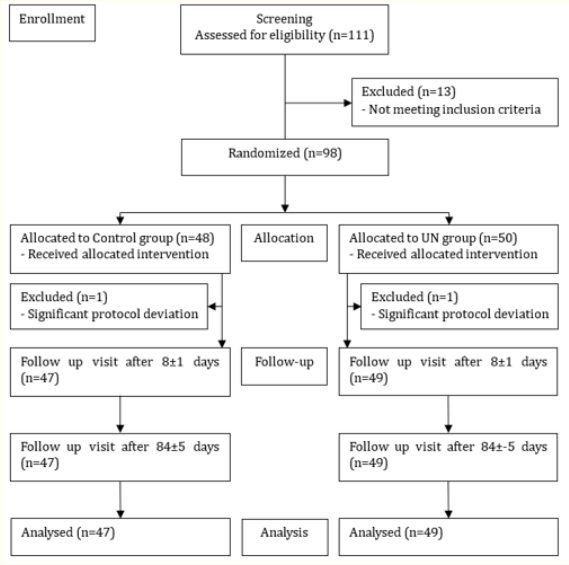
Visit 3 was an outpatient visit, scheduled for day 84 ± 5. Physical evaluation, review of concomitant therapy, urinanalysis, and bacteriological examination were performed as described above. Compliance with exclusion criteria was assessed. Once more 100 mm VAS scale, VAS QoL and ACSS scores were recorded. Entries in urinary diary and patient's diary were reviewed, all adverse events were registered. Patients returned remaining drugs or food supplements, compliance to therapy was determined.

If a patient had no AEs/SAEs, participation in the study was considered completed after the third study visit. If a patient withdrew from the study due to an AE/a SAE, she was followed up until the AE/SAE resolved or became chronic or stabilized. Therapy to treat the new condition was carried out in accordance with the treatment standards adopted in the Russian Federation. In case of repeated exacerbation of LUTI an immediate additional visit was carried out. Procedures at relapse visit were identical to procedures at visit 2, with the exception of questionaries, that at additional visit weren't required. In case of relapse, fosfomycin trometamol 3.0g was allowed for administration. If a face-to-face consultation with a doctor was not possible, the patient could independently take fosfomycin trometamol 3.0g. Each recurrence of symptoms was considered an exacerbation case. The patient was given the date of the next visit and a notice to bring the patient's diary.

A post-relapse visit was carried out 7 days ± 1 day after the relapse visit. During the post-relapse visit the same procedure were carried out as at the relapse visit.

Results

A total of 111 candidates signed ICF and went through the screening procedure. 13 participants were found non-compliant with the inclusion criteria, thus a total of 98 patients were randomized into 2 groups. Due to significant protocol deviation 1 participant in each group was excluded from the trial. 96 participants received full treatment and completed all procedures in accordance with the protocol. Data from these 96 participants was used for the per protocol (PP) efficacy analysis.



Figure

Baseline characteristics of study participants are summarized in table 1.

	UN group	Control group
Number of participants	49	47
Age (years)	54,2 ± 16,5	45,9 ± 16,3
Weight (kg)	68,8 ± 12,9	64,1 ± 9,9
Height (cm)	163,7 ± 6,9	166,2 ± 4,6
BMI (kg/m^2)	25,1 ± 4,9	23,2 ± 3,8

Table 1: *Participant baseline demographic data.*

Endpoints

The proportion of patients who did not have relapses of the disease at visit 3 in the UN group significantly exceeded the corresponding proportion of patients in the control group: 77,6% versus 19,2%, respectively ($p < 0,0001$). Statistical calculations were performed using Fisher's exact test.

The mean recurrence rate of cystitis between first and last visit is presented in the table 2. The difference between UN group and control group was 0,78 ± 0,63 and reached statistical significance ($p < 0,0001$). Comparison was performed using the Wilcoxon test.

Group	UN (N = 49)	Control (N = 47)	Statistics
Mean ± SD	0,29 ± 0,58	1,06 ± 0,67	p < 0,0001
Median	0	1	
Min - Max	0 - 2	0 - 2	
95% CI	0,12 - 0,45	0,87 - 1,26	

Table 2: *Recurrence rate of cystitis between visit 1 and visit 3.*

100 mm VAS scale was used for evaluation of urinary discomfort in the first three days. Totals of several measurements were compared between groups for each parameter. Difference in pain intensity from baseline was determined via the Wilcoxon test, difference in urinary urge was calculated using Wilcoxon test and Student's T-test and change in urinary frequency severity via Student's t-test. Results are presented in table 3, changes in total scores did not reach statistical significance.

100 mm VAS scale	UN	Control	Statistics
Pain intensity	232,3 ± 79,0	241,9 ± 91,6	p = 0,53
Urinary urge	214,3 ± 85,4	219,9 ± 85,3	p = 0,75
Urinary frequency severity	203,7 ± 100,2	179,6 ± 103,9	p = 0,25

Table 3: *Change in 100 mm VAS scale results.*

Frequency of urination based on the urination diary on days 1, 2 and 3 of observation in the groups did not differ significantly (Table 4). Statistical calculations were performed using covariance analysis.

ACSS is self-reporting questionnaire for the diagnosis of acute uncomplicated cystitis, consisting of 18 questions, divided in 5 domains [28]. "Typical" domain includes questions about the most common symptoms. Within the group comparison for both time pointes revealed

	Urination frequency		Mean urine volume (ml)	
	UN	Control	UN	Control
Day 1	12.8 ± 3.5	13.7 ± 3.4	190,4 ± 281,2	146,7 ± 56,2
Day 2	10.5 ± 3.0	11.3 ± 3.3	193,4 ± 172,9	169,7 ± 46,3
Day 3	9.2 ± 2.9	10.4 ± 3.5	207,6 ± 154,8	186,0 ± 56,2

Table 4: *Urination diary data.*

statistically significant changes in both groups (Table 5), while no significance was seen in head to head comparison, indicating that on average both groups were comparably successful in addressing the acute cystitis symptoms. Differential" domain grades symptoms regarding other genitourinary problems [29], in third domain impact on QoL is determined. According to the outcomes of the ACSS questionnaire, changes in the QoL between visit 1 and visits 2 and 3 reached statistically significant difference in both groups, at all timepoints.

Fourth domain includes question about additional aspects, such as pregnancy or diabetes mellitus. At the follow-up visits extended version of the questionnaire was used, that includes also the "differential" domain. Change in the QoL assessment subscale and symptom dynamics assessment subscale differed significantly between the groups, at both follow up visits, while the difference for the differential symptoms subscale differed significantly only when comparing scores from visit 1 to visit 2. Other comparisons between the groups did not reach statistical significance. Statistical calculations were performed using the Wilcoxon test.

Typical symptoms UN		Group		Comparison
		Control		
Visit 1	Mean ± SD 95% CI n	11,9 ± 3,9 10,8 - 13.0 49	13.6 ± 2.5 12,8 - 14,3 47	
Visit 2	Mean ± SD 95% CI n	2,8 ± 2,4 2,1 - 3,5 49	4,7 ± 4,3 3,4 - 6,0 47	
V1 vs. V2	Mean ± SD 95% CI n	9,1 ± 4,6 7,8 - 10,4 49 p < 0,0001	8,9 ± 4,8 7,4 - 10,3 45 p < 0,0001	p = 0,99; Z = 0,01
Visit 3	Mean ± SD 95% CI n	1,3 ± 1,8 0,8 - 1,9 49	2,4 ± 2,7 1,6 - 3,2 45	
V1 vs. V3	Mean ± SD 95% CI n	10,6 ± 4,6 9,3 - 11,9 49 p < 0,0001	11,1 ± 3,4 10,0 - 12,1 45 p < 0,0001	p = 0,37; Z = 0,89

ACSS Differential symptoms UN		Group		Comparison
		Control		
Visit 1	Mean ± SD 95% CI n	0,1 ± 0,4 0,0 - 0,3 49	0,1 ± 0,3 0,0 - 0,2 47	
Visit 2	Mean ± SD 95% CI n	0 ± 0 - 49	0,1 ± 0,2 0,0-0,1 46	
V1 vs. V2	Mean ± SD 95% CI n	0,1 ± 0,4 0,0 - 0,3 49 p = 0,0313	0,0 ± 0,4 -0,1 - 0,1 46 p = 1,0	p = 0,0429; Z = 2,02
Visit 3	Mean ± SD 95% CI n	0 ± 0 - 48	0 ± 0 - 45	
V1 vs. V3	Mean ± SD 95% CI n	0,1 ± 0,4 0,0 - 0,3 48 p = 0,0313	0,1 ± 0,3 0,0 - 0,2 45 p = 0,5	p = 0,18; Z = 1,34
ACSS Quality of Life UN		**Group**		**Comparison**
		Control		
Visit 1	Mean ± SD 95% CI n	7,8 ± 1,6 7,3 - 8,3 49	8,0 ± 1,3 7,6 - 8,4 47	
Visit 2	Mean ± SD 95% CI n	1,9 ± 2,1 1,3 - 2,5 49	3,1 ± 2,4 2,5 - 3,8 47	
V1 vs. V2	Mean ± SD 95% CI n	5,9 ± 2,7 5,2 - 6,7 49 p < 0,0001	4,9 ± 2,7 4,1 - 5,6 47 p < 0,0001	p = 0,0404; Z = 2,05
Visit 3	Mean ± SD 95% CI n	0,8 ± 1,4 0,4 - 1,2 49	2,0 ± 1,9 1,4 - 2,6 45	
V1 vs. V3	Mean ± SD 95% CI n	7,0 ± 2,1 6,4 - 7,6 49 p < 0,0001	6,0 ± 2,4 5,2 - 6,7 45 p < 0,0001	p = 0,0210; Z = 2,31

Dynamics score UN		Group		Comparison
		Control		
V1 vs. V2	Mean ± SD 95% CI n	0,9 ± 0,8 0,7 - 1,1 48 p < 0,0001	1,5 ± 1,0 1,2 - 1,7 46 p < 0,0001	p = 0,0029; Z = 2,98
V1 vs. V3	Mean ± SD 95% CI n	0,5 ± 0,7 0,3 - 0,6 48 p < 0,0001	1,2 ± 1,1 0,9 - 1,5 45 p < 0,0001	p = 0,0005; Z = 3,49

Table 5: *ACSS subscales outcomes.*

Change in QoL was significantly different also when assessed through the VAS QoL scale (Table 6). Statistical calculations were performed using the Wilcoxon test; verification result for normality using the Shapiro-Wilk test. Both groups reached statistically significant difference at both follow up visits, however between group comparison confirmed that the change was more pronounced in UN group (p = 0,0407 at visit 2 and p = 0,0457 at visit 3).

VAS QoL UN		Group		Compari-son
		Control		
Visit 1	Mean ± SD 95% CI N	32,4 ± 7,2 30,4 - 34,5 49	33,4 ± 5,3 31,9 - 35,0 47	
Visit 2	Mean ± SD 95% CI N	4,7 ± 6,6 2,8 - 6,6 49	10,1 ± 11,5 6,8 - 13,5 47	
Visit 1 vs. Visit 2	Mean ± SD 95% CI N	27,8 ± 10,6 24,7 - 30,8 49	23,3 ± 12,0 19,8 - 26,8 47	p = 0,0407, Z = 2.05
Visit 3	Mean ± SD 95% CI N	1,7 ± 4,3 0,4 - 2,9 49	5,8 ± 7,4 3,6 - 8,0 47	
Visit 1 vs. Visit 3	Mean ± SD 95% CI N	30,8 ± 8,9 28,3 - 33,3 49	27,6 ± 8,8 25,0 - 30,2 47	p = 0,0457, Z = 2,00

Table 6: *VAS QoL outcomes.*

UN did not adversely affect the vital functions of patients, including systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and body temperature. The frequency of concomitant diseases and the concomitant drug use did not differ between the two groups. The patients tolerated the treatment well. All participants consumed the initial antibiotic treatment, while 98% of the participants in the UN group consumed all prescribed dosages of the food supplement.

2 AEs were recorded in 2 (3.4%) patients in the UN group. One AE was an allergic reaction to UN resulting in the patient terminating the participation in the study ahead of schedule. The connection between the supplement and the reaction was marked as probable. Other

AE consisted of complaints of rare micturition urgencies, frequent urination and nausea after taking the food supplement for 30 minutes, which resolved on its own and the patient continued to participate in the study.

Laboratory analysis revealed a number of abnormalities in the complete blood count in 1 patient of the UN group and in 1 patient of the control group; in 2 patients of the UN group in the biochemical blood test; in 25 patients of the UN group and in 23 patients of the control group in the urinalysis. Abnormalities in blood tests were clinically insignificant and were comparable between groups. Urinalysis deviations were manifestation of the underlying disease of the lower urinary tract.

Discussion

Recurring LUTIs in women not only have detrimental effects on individual health but also present a significant burden to the public health system. The adverse impact on patients' quality of life emphasizes the urgent need for research on adjunctive therapies [30]. Our study was investigating the efficacy and safety of the food supplement UN in women with acute cystitis.

Based on EAU guidelines on urological infections, fosfomycin trometamol should be considered a first line treatment in uncomplicated cystitis [31]. Review of studies on fosfomycin trometamol suggests that clinical success rate after a single dose of the antibiotic varied between 76,0 and 88,2%, as recorded approximately a week after the administration. Fajfr., *et al*. looked into long term effects of fosfomycin trometamol and concluded that oral treatment is highly effective in uncomplicated urinary tract infections, while in recurrent infections the recurrence of the disease becomes relatively higher [32]. High recurrence rate in control group indicates that population in our study was prone to recurrence of the cystitis, while supplementation with UN could significantly suppress the occurrence of infection episodes.

In practice, the assessment of treatment efficacy relies on standardized medical criteria, whereas patients play a crucial role in providing insights into their individual perceptions of the treatment and its impact on their daily functioning. Given potential disparities between objective parameters and individual perceptions, it is imperative to systematically document the influence on QoL [28]. Statistically significant enhancements in QoL measurements, as evidenced here by various assessment tools, affirm that supplementation with UN effectively addresses the individual's perception of the conditions' impact on life.

Alternative approaches towards LUTI are being actively promoted, but often lack sound scientific background [33]. Research on food supplements in relation to LUTI is focused mainly on the prevention of the recurrence of the cystitis. Among the most researched approaches in the category is supplementation with cranberry based products. Recent review of clinical research confirmed that cranberry products can prevent the disease in women with frequent LUTI [34]. Our results confirm the previously seen preventive power of cranberry based food supplements. In recent years, the combination of cranberries and D-mannose has undergone testing in various populations, providing us with a more comprehensive understanding of the combination's mechanisms and expanding the base of positive results associated with its functionality [35-37]. To the best of our knowledge, our trial stands as the initial endeavor to demonstrate the enduring advantages of scheduled supplementation every other week. This approach has been associated with a significantly reduced rate of recurrence and an enhanced quality of life.

Future research initiatives on UN could investigate effects of various supplementation protocols. Furthermore, critical consideration should be done regarding predispositions among participants towards recurrent cystitis.

Conclusion

This study has shown that the UN food supplement taken daily, every alternating week, for 3 months is an effective and safe option in addressing patients with LUTI. A significantly reduced relapse rate, as compared to control group, opens a new possibility for positioning this food supplement as a relapsing cystitis prevention product.

Supplementation with UN does not adversely affect vital functions of patients with relapsing cystitis and has no effect on parameters of biochemical blood tests, complete blood counts and urinalyses during a 3-month treatment course. The ACSS assessment showed statistically significant differences in QoL and symptom dynamics domains between groups in favor of UN. The VAS QoL questionnaire assessment also demonstrated a statistically significant benefit of UN when compared to control.

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Conflict of Interest

No financial interest or any conflict of interest exist.

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