ORIGINAL ARTICLE

Cranberry Extract And D-Mannose Combination in the Prevention of Urinary Tract Infections in Women: A Prospective, Observational Study in a Tertiary Care Hospital

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ABSTRACT

Objectives: To compare the efficacy and safety of a combination of cranberry extract and D- mannose with cranberry extract alone in the prevention of urinary tract infections in women. **Methods:** In this prospective observational study involving 150 patients with urinary tract infections (UTIs), after receiving antibiotic treatment, 147 patients progressed to phase two. These patients were then randomly assigned to two groups: one group received a combination of cranberry extract and D-mannose, while the other group received cranberry extract alone. The treatment was administered for a duration of three months. **Results:** Three participants were lost to follow-up due to experiencing a mild rash and non-compliance. Additionally, 13 patients required a second course of antibiotic therapy in order to proceed to phase two. At the end of the three-month period, participants in Group B exhibited a higher rate of urinary tract infection recurrence compared to those in Group A, and this difference was statistically significant with p-value <0.05. Furthermore, 5.4% of participants in Group A reported adverse effects such as nausea, diarrhoea and abdominal pain, which were more prevalent than in Group B. **Conclusion:** This study provides compelling evidence to suggest that the synergistic combination of Cranberry Extract and D-mannose exhibits considerable promise in mitigating the risk of urinary tract infections (UTIs) in the female population. The findings underscore the inherent efficacy of this combination as a preventive modality against UTIs in women.

Malaysian Journal of Medicine and Health Sciences (2024) 20(SUPP13): 61-65.doi:10.47836/mjmhs.20.s13.13

Keywords: cranberry extract, d mannose, urinary tract infection

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INTRODUCTION

Urinary tract infections (UTIs), although being the subject of intensive research for several years, are still the most frequent infectious disease in women, a major driver of morbidity and health associated expenditure, a contributor to decreased quality of life and a significant social burden. While both males and females can develop UTIs, they are more prevalent in females due to anatomical differences that make it easier for bacteria to reach the bladder. Based on clinical and biochemical criteria, UTIs are classified into lower (cystitis) and upper (pyelonephritis) infections (1,2).

The symptoms of UTI in females include frequent and strong urge to urinate, burning sensation or pain during urination, cloudy or bloody urine, pelvic or flank pain, and fever 3. Management of urinary tract infections with antibiotics is the standard practice. Antibiotic resistance makes treating UTIs much more complex. As the prevalence of recurrences after a first episode of UTI is rated at 25-50% in previous studies, there is a growing concern about the adverse effects of the classic antimicrobial treatment of the acute UTI and also of the recurrence prophylaxis (3). Therefore, it is important go for additional therapy that would reduce UTI incidence, costs, and antibiotic use, while improving antimicrobial stewardship (4).

Proanthocyanidins, antioxidants found in cranberry extracts, are thought to have an antiadhesive activity that keeps bacteria from sticking to the uroepithelial cells that line the bladder wall (5,6). D-mannose is a type of sugar that also plays a role in the antiadhesion of uropathogenic Escherichia coli (7,8). The combination of cranberry extracts and D-mannose, available as a fixed dose combination of cranberry extract 140 mg and D-mannose 2g, prevents the adhesion of p-fimbriated E. coli on cells of the bladder (9). This non-antimicrobial combination of Cranberry extract and D-mannose helps to prevent UTIs and subsequent infections, the

emergence of resistance or any adverse side effects that may result from using antibiotics every time in case of UTI recurrence. Cranberry extract and D-mannose have also been proved to be individually effective in the management of RUTIs (10).

A review article by Lenger Stacey M et al., in 2022 compared D-mannose with placebo for urinary tract infections in adult women with recurrent UTI's. D-mannose was protective against recurrent UTI's and found to be as effective as antibiotics. Also, D-mannose was reported to have mild adverse effects, with just a few users reporting diarrhoea and nausea (11). A systematic review and meta-analysis of ten studies reported the efficacy of Cranberry extract, with eight articles comparing Cranberry extract with placebo and two comparing it with antibiotics. In this review, five studies reported reduced incidence of RUTI with Cranberry extract in comparison to placebo and better acceptability than antibiotics (12). One clinical trial by Genovese et al., 2017 also compared D-mannose in combination with other naturally available compounds like berberine, uva ursi, birch and forskolin. These combinations of D-mannose reduced the incidence of cystitis during the treatment phase and also in the follow-up phases (13).

Several research endeavours have scrutinized the individual efficacy of cranberry extract, with limited exploration into their combined effectiveness. Furthermore, these studies have predominantly concentrated on comparing them against a placebo. To date, no study has compared the efficacy of a combination of cranberry extract and D-mannose with cranberry extract alone in female patients for preventing recurrent UTIs. Hence this study aims to evaluate how effective the combination of cranberry extract and D-mannose is in preventing recurrent UTIs in women following their initial infection.

MATERIALS AND METHODS

It is a Prospective Observational study conducted over a period of 6 months July 2023 to December 2023 in Outpatient department, Department of Urology in Saveetha Medical college and Hospital, Chennai. After obtaining approval from the Institutional Ethics Committee, Saveetha Medical college and Hospital (IEC- reference number: 111/06/2023/IEC/SMCH), the study has been conducted in accordance with Good Clinical practice and Declaration of Helsinki.

The sample size was calculated using the formula n = $Z2((1- \alpha)/2) \times p (1- p) /d2$. The prevalence of recurrent UTI in women was derived from study by Witteman et al (14). One hundred and fifty patients above 18 years diagnosed with uncomplicated UTI were assessed for eligibility and included in the study after getting written informed consent. Whereas Pregnant women and lactating women, Patients who had symptoms of a systemic inflammatory disease, gynaecological disorders, any anatomical malfunction, operated previously on kidney / bladder for kidney stones, patients with autoimmune disease /other neurological disease and patients on urinary catheter were excluded from the study.

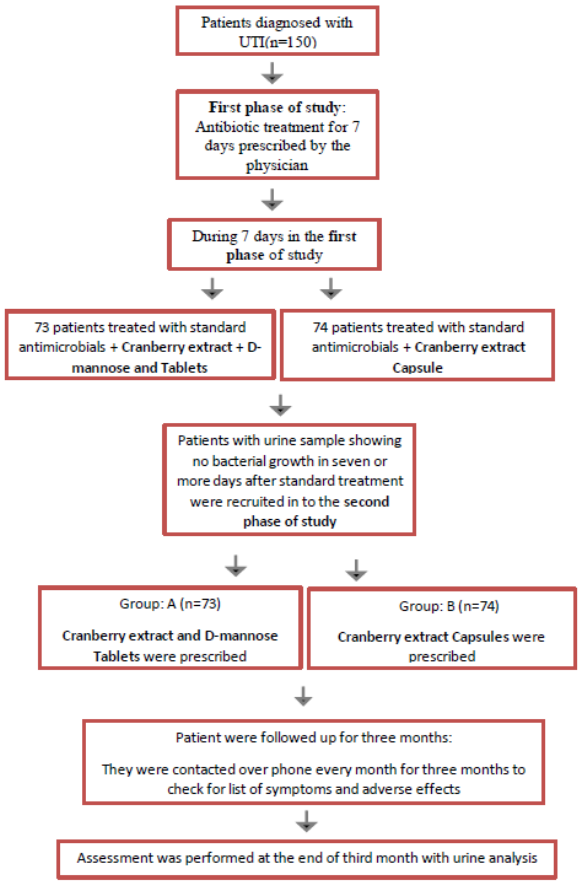
The study was divided into two phases. Study participants underwent thorough evaluation obtaining complete medical history including detailed past, menstrual and obstetric history and clinical examination. Complaints were recorded at the baseline visit using questionnaire.

A validated questionnaire had a list of 4 characteristic symptoms of UTI (pain in the lower abdomen, burning micturition, urinary frequency and urgency) and numbering their intensity from 0 to 3(absent, mild, moderate, strong) and other 4 questions pertaining to how impairing those symptoms are for the patients with four degrees of intensity. The total symptom severity score is categorized as (mild (0-8), moderate (9-16) and severe (17-24)) (15). Urine analysis including both urine routine and urine culture were done in all patients.

Patients were started on antimicrobial therapy as per physician's advice. Patients were evaluated with the same questionnaire to assess the symptoms severity and urine analysis after 7 days of antibacterial therapy. 13 patients with positive urine culture underwent 7 more days of antibacterial therapy. 147 participants with negative culture entered the second phase. Study participants were randomized into two groups containing 73 patients in group A and 74 in group B by systemic randomization with the help of computer-generated tables.

Group A patients were prescribed with 900 mg cranberry extract and D- mannose tablets once daily in the morning after food for 3 months, Group B patients were prescribed only 300 mg cranberry extract capsules once daily in the morning after food for 3 months. Follow up performed every month for 3 months through phone call assessing symptoms and adverse effects and urine analysis done at the end of 3rd month. The same questionnaire was used five times to evaluate clinical manifestation. Participants were encouraged to contact if they had any increase in severity of symptoms or any adverse effects at any point during the study. The objective of the study is to compare the effect of Cranberry extract and D-mannose and cranberry extract alone in culture negative patients following active treatment on persistence and recurrence in the symptoms of the UTI when given for 3months. For safety analysis, occurrence of any adverse reactions during the study were noted.

METHODOLOGY FLOWCHART



Statistical Methods:

The data were entered into MS Excel 2007 and further analysed using SPSS (version 20.0; SPSS Inc., Chicago IL, USA). For descriptive analysis, the categorical variables were analysed using frequency and percentages and the continuous variables were examined by calculating mean ± Standard Deviation. For inferential analysis, the numerical data were analysed using the 't-test and, the categorical data were analysed using the Chi-square test. The p value <0.05 considered statistically significant.

RESULTS

150 study participants were females with mean age of 43.72 years (minimum age of 23 years and maximum of 74 years). All the participants had increased leukocytes with their culture showing Escherichia coli bacteria (Table 1). All had undergone baseline clinical examination and investigations, where all the study participants had a mean total severity score of 21.63 with minimum score of 13 and maximum score of 24 equating to the categories of moderate and severe. Study participants were prescribed appropriate antibiotic therapy for a period of 7 days as per the physician's advice. 74 participants were prescribed with Nitrofurantoin, 26 with Norfloxacin, 12 participants prescribed with Cefpodoxime proxetil tablets and the remaining patients with Amoxiclav tablet (Figure 2

Patients underwent symptom enquiry and urine analysis after 7 days of active treatment where the reduction in symptom severity was found to be statistically significant (p= 0.049). the symptom intensity reduced from severe and moderate to mild (Table 2)

Table 1: Baseline characteristics of study participants

Characteristic	Study Participant (n)
Age Mean (SD) Median (min, max)	43.72 (12.34) 43 (23, 74)
Urine Culture E coli	150
Urine Routine Leukocytes	150

Table 2: Treatment evolution- Reduction in symptom severity at the end initial treatment

Variable	Total severity score Baseline	Total severity score Post Treatment	Reduction	P value
Mean (SD)	21.63 (2.09)	1.29(3.29)	-20.34	0.049

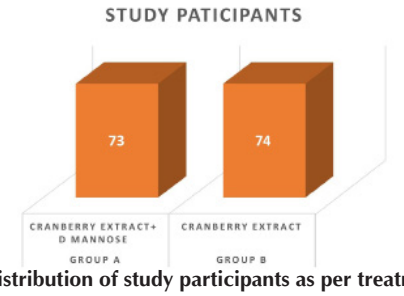


Figure 1: Distribution of study participants as per treatment arm

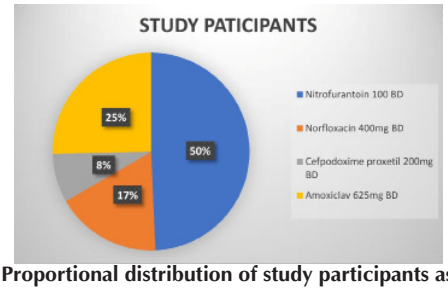


Figure 2: Proportional distribution of study participants as per antibiotics treatment

Table 3: Treatment evolution- Urine Analysis at the end of initial antibiotic treatment

Urine Analysis	Baseline n (%)	Post treatment n (%)	P value
Urine routine - Pus cells	138 (92%)	22 (14.5%)	0.002
Urine Culture- Positive (E coli)	150 (100%)	13 (9%)	0.003

Urine analysis showed that 22 (14.5%) had increased in leukocytes and 13 participants (9%) still showed the presence of E. coli in their culture. The treatment evolution was found to be statistically significant (p=<0.05) after the 7 days course of antibacterial therapy (Table 3). 13 patients who still showed presence of organisms in urine culture received a 2nd course of antibiotic therapy for 7 more days. 3 participants withdrew their consent where one participant had mild rash and the other two failed due to loss of compliance.

Table 4: Phase – 2 Comparison of Symptom severity score between both groups, cranberry extract plus D-mannose versus cranberry extract.

Severity Score	Group A (n=73)	Group B (n=74)	P value
Total severity score Baseline Mean (SD)	0.01 (0.11)	0.02 (0.16)	0.651
Total severity score At the end of 2 months Mean (SD)	0.22 (1.39)	1.02 (3.25)	<0.001
Total severity score At the end of 3 months Mean (SD)	0.39 (1.96)	5.68 (9.42)	<0.001

Table 5: Comparison of urine analysis results between both groups at the end of 3rd month, cranberry extract plus D-mannose versus cranberry extract

Urine Analysis	Group A (n=73)	Group B (n=74)	P value
Urine routine - Pus cells	5 (6%)	22 (30%)	0.038
Urine Culture- Positive (E coli)	3 (4%)	21 (28.3%)	0.014

As mentioned earlier, study treatments were given to 147 participants who entered the 2nd phase of the study with 73 participants in Group A and 74 in Group B. Participants had symptom recurrence after 30 days in both groups which increased in the 3rd month on study medication. The group that had taken both Cranberry extract and D-Mannose tablet had less recurrence of the symptom with their severity ranging from mild to moderate at the end of 2nd and 3rd month. Whereas group B had more recurrence starting from 2nd month and increasing at the end of the 3rd month with mean and standard deviation of 5.68 (9.42). Same results were seen in urine analysis of Group B where 21 participants had positive urine culture with E. coli (Table 4 & 5). Thus, the recurrence of UTI was significantly low (p=<0.05) in group taking both cranberry extract and D-mannose tablet. 6 Participants who were on both cranberry extract and D mannose reported with nausea, diarrhoea and abdominal pain and 2 patients from the other group had complaints of nausea and diarrhoea.

DISCUSSION

Cranberry products and extracts have been studied since early 90's on their beneficial effects on treatment of UTI and also in their prophylaxis. Their phenolic content increases the pH of urine that helps in their bacteriostatic property and also the nonenzymatic production of nitric oxide helps in their antimicrobial action as one of the earlier proposed mechanisms (16,17). A newer mechanism is the anti-adhesive mechanism of Proanthocyanidins (PAC) in the extract help in preventing the bacteria to attach to uroepithelial cells of the bladder.

Similarly, the mechanism of action of D mannose is not very well understood, but invitro studies suggests that it has a similar antiadhesive mechanism. D mannose is the primary receptor binding site for E. coli to bladder epithelium. There are many studies that showed the effectiveness of D mannose in urinary tract prevention and as an adjuvant in treating UTI. But there are very few studies on effectiveness of their combination and no studies comparing the combination with cranberry extract. Therefore, we performed this study to show the effectiveness of their combination against just cranberry extract in preventing further UTI in women with uncomplicated UTI, which is a growing concern as the recurrence after the first episode is evidenced in more than half of them.

Cranberry extract and D-mannose have been proved to be individually effective in the management of RUTIs. A systematic review and meta-analysis by Jepson RG et al., 2012 included 24 studies with a total of 4473 participants concluded that cranberry extracts alone is not efficient to prevent the UTI recurrence. This conclusion fits with our study where the cranberry extract alone did not prevent the recurrence of UTI (18).

Only two clinical trials have investigated the combination of cranberry extract and D-mannose in RUTI. In a prospective study by Efros et al., 2010 (1) involving 28 women, the liquid cranberry-containing medication with a blend of Cranberry extract concentrate and D-mannose was well tolerated and safe; it also prevented 91% of patients from developing RUTI for three months. This combination product was beneficial for avoiding RUTIs and had sufficient power to eradicate lower uncomplicated UTIs. In another clinical trial by Radulescu et al.,2020, a combination of cranberry extract and D-mannose increased bacterial sensitivity to antibiotics. The recurrence rate was 4.17% when cranberry extract plus D-mannose was added to standard antibiotic treatment, lower than in the placebo arm, the combination cranberry extract and D-mannose was beneficial in avoiding RUTIs, had a higher cure rate than a placebo and was tolerable and safe. In both the above-mentioned clinical trials, the combination of cranberry extract and D-mannose had been compared with placebo (19). These results are similar to our study where the group that received the combination of cranberry extract and D mannose had a recurrence rate of 4% compared to the group with cranberry extract alone where the recurrence was 28%.

CONCLUSION

The combination of Cranberry extract and D mannose tablet has proved to be a promising adjuvant for preventing UTI in females in whom UTI recurrence is of the growing concerns. The efficacy shown by the combination in this study is highly significantly improved in comparison with cranberry extract alone.

ACKNOWLEDGEMENT

I am grateful and obliged to our respectable medical director, dean (medical), medical superintendent for their constant support and permission to carry out this study.

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