

A Randomized, Double Blind, Controlled, Dose Dependent Clinical Trial to Evaluate the Efficacy of a Proanthocyanidin Standardized Whole Cranberry (*Vaccinium macrocarpon*) Powder on Infections of the Urinary Tract

K. Sengupta¹, K.V. Alluri¹, T. Golakoti¹, G.V. Gottumukkala¹, J. Raavi¹, L. Kotchrlakota¹, S.C. Sigalan¹, D. Dey², S. Ghosh² and A. Chatterjee^{3,*}

¹Alluri Sitarama Raju Academy of Medical Sciences (ASRAM) Eluru, Andhra Pradesh, India, ²University of Connecticut, Storrs, CT, USA, ³Creighton University School of Medicine, Omaha, NE, USA

Abstract: Urinary tract infections (UTIs) represent a recurrent health problem especially for women. More than 50% of women will suffer from a UTI at least once in their lifetime. Cranberries have long been used for their beneficial effects in preventing symptomatic UTIs in several published studies. However, cranberry products used in these clinical studies do not indicate the amount of active ingredients delivered that help to prevent UTIs. Therefore, a dose-dependent study was designed to understand the impact and safety profile of a standardized cranberry product (Proanthocyanidins Standardized Whole Cranberry Powder, PS-WCP) on reducing the recurrences of symptomatic UTI in culture-positive subjects. A 90-day randomized clinical trial including an untreated control group with a total of 60 female subjects between 18-40 years of age was conducted. Study subjects were randomly selected and assigned to three groups including an untreated control group (n=16), a low dose (500 mg daily, n=21) and a high dose (1000 mg daily, n=23) treatment group. The safety of PS-WCP was assessed by evaluation of biochemical and hematological parameters on days 10, 30, 60 and 90 during the study, comparing the values with those at the baseline. Occurrence of UTI at baseline and during the follow-up period was characterized by the presence of symptoms and *Escherichia coli* in the culture of urine samples. The statistical analysis used was ANOVA. At the end of the 90-day treatment period, no significant changes were observed in the hematological and serum biochemical parameters. At the end of the study, change in the presence of *E. coli* in the untreated control group was not significant (p=0.7234), whereas, there was significant reduction (p<0.05) in the subjects positive for *E. coli* in both the high dose and low dose treatment groups, compared to baseline evaluation. Symptomatic relief was also reported in the low and high dose treatment groups, while none was reported by subjects in the untreated control group. In conclusion, PS-WCP was effective in safely reducing the number of *E. coli* positive subjects at both the 500 mg and 1000 mg dose levels and in ameliorating the symptoms of UTI in these subjects. Therefore, a daily dose of 500 mg or 1000 mg of PS-WCP may be considered as an adjunct to antibiotic prophylactic therapy against recurrent UTIs.

Keywords: UTI, prevention, clinical, standardized, cranberry.

INTRODUCTION

Urinary tract infections (UTIs) are a serious, recurrent global health problem of millions of people [1]. Women are significantly more likely to experience UTIs than men and almost half of all women will experience at least 1 UTI during their lifetime, their high prevalence causing remarkable costs to healthcare systems [2]. The most common pathogen responsible in approximately 80% cases is *Escherichia coli* [1, 3]. UTIs are typically treated with antibiotics, but emerging antimicrobial resistance warrants the need for alternative therapeutic and preventative strategies [4].

Cranberries (*Vaccinium macrocarpon*) have been used for many centuries for their medicinal properties [5], and a number of reports are available in support of their therapeutic potential against UTIs [6-8]. The beneficial mechanism was historically thought to be due to fruit acids causing a bacteriostatic effect in the urine [6]. However, a group of proanthocyanidins (PACs) with A-type linkages have been

isolated from cranberries which exhibit bacterial antiadhesion activity against both antibiotic susceptible and resistant strains of uropathogenic *E. coli* [6, 9]. Cranberries thus appear to work by inhibiting the adhesion of uropathogenic *E. coli* to the uroepithelium, impairing colonization and subsequent infection [9]. Cranberry PACs are a complex mixture of doubly linked polymeric compounds with epicatechin monomeric units linked to each other with the more common B-type linkage and the unique A-type linkage. Several recent studies have shown that consumption of cranberry products can reduce bacteriuria and prevent symptomatic recurrences of UTI in adult women [10-12]. However, some studies have indicated that the prolonged consumption of cranberry juice is unacceptable to many patients because of its cost, highly acidic taste and caloric load [8, 13, 14]. In this respect, capsules of cranberry juice concentrate or powder could be the better-tolerated alternative and also more cost-effective than cranberry juice [15]. Since cranberry products vary in phytochemical content depending on variety, location and production run, it is necessary to use a product that is standardized for the bioactive ingredients that can be measured objectively [16]. Using random commercial samples with unknown amounts of bioactive ingredients can affect the out-

*Address correspondence to this author at the Dept. of Pediatrics, Creighton University School of Medicine, 601 N 30th St., Suite 2321, Omaha, NE 68131; Tel: (402) 280-1238; Fax: (402) 280-1234; E-mail: a chatter@creighton.edu

comes of clinical studies. It is also critical to establish the relationship between the samples used in clinical studies and the products available commercially, so that the results of clinical studies can be applied to the products available on the market. Therefore, in the present randomized, controlled study, we designed a protocol to assess the efficacy and safety of a commercially available PACs standardized whole cranberry powder (PS-WCP) against recurrent UTIs in women following supplementation over a period of 90 days. Clinical examinations as well as microbiological and biochemical assessments were conducted on day 0, 10, 30, 60 and 90 of treatment. All adverse events were also recorded on a daily basis.

SUBJECTS AND METHODS

Test Substance

A proanthocyanidin standardized whole cranberry powder (PS-WCP) encapsulated, obtained from Decas Botanical Synergies (Carver, MA) was used for this study. According to the information provided by the supplier, PS-WCP is standardized to 1.5% proanthocyanidins using a proprietary process. The specific lot of sample used for the clinical trial was verified for its PACs content by a third party independent laboratory (Brunswick Laboratories Inc.) using the USDA approved HPLC method [17]. According to Gu et. al., cranberries contain 51-65% procyanidin type-A linkages [18]. The proanthocyanidins profile of the sample used in this study is as indicated in Table 1. No preservatives, flavoring or coloring agents are used during the production of this powder.

Table 1. Detailed Profile of the Sample Used for Clinical Trial. Table Indicates Composition of Monomers, Dimers, Trimers Upto Polymers, as Measured Using HPLC at Brunswick Labs

PACs	mg/g
1mers	0.54
2mers	1.78
3mers	0.73
4mers	0.37
5mers	0.14
6mers	0.26
7mers	0.02
8mers	0.17
9mers	0.32
10mers	0.45
>10mers	9.81
Total	14.50

Safety Studies

Before using the PS-WCP for a human clinical trial, a thorough literature review was conducted into the safety of

cranberry and cranberry-based products. This review clearly indicated that cranberry and cranberry-based products have been safely consumed over hundreds of years without any significant serious adverse effects. Since this was a standardized powder and no safety data were provided by the supplier specifically for this product, an acute oral LD50 test using the up and down procedure in female rats per the Organization for Economic Cooperation and Development (OECD) guidelines, was conducted. This study indicated that acute oral LD50 in female Sprague Dawley rats is greater than 5g per kilogram of body weight.

Recruitment of Study Subjects

This trial was performed at Eluru, Andhra Pradesh in India. A total of 225 female patients were assessed for enrollment based on their symptoms, including history of frequency and painful urination. Thereafter, all the volunteers were screened based on the inclusion-exclusion criteria and sixty patients were finally selected for the trial.

Female patients in the age group of 18 to 40 years, with a history of painful urination and frequency, passing blood in the urine or pain in the suprapubic area, and with a negative pregnancy test were included in the study. Patients who had either taken antibiotics within the previous 48 hours or were catheterized within the previous 2 weeks were excluded from the study. Patients with diabetes, history of cardiovascular diseases, symptoms of pyelonephritis and stones in the urinary tract (kidney, bladder or ureter) were excluded. The purpose and methods of this study were explained to all subjects and they agreed to participate in this clinical trial by providing written informed consent.

Study Design

A total of 60 women participants with a history of recurrent UTIs, and currently culture positive with mild symptoms of UTI, were randomly selected to participate and assigned to one of three groups. Randomization was performed by opening sealed envelopes in numbered sequence prepared by an individual not involved in the study, and prepared from a computer-generated random numbers program. The treatment codes were confidential and held by the clinical trial pharmacist. The participants were randomly distributed into three groups; untreated control group (n=16), cranberry low dose (500 mg/day) (n=21) group in which the participants received encapsulated 250 mg of PS-WCP twice daily; and cranberry high dose (1000 mg/day) (n=23) group, in which the participants received encapsulated 500 mg of PS-WCP twice daily. Carboxymethylcellulose was used as a filler in the 250 mg capsules to match with the 500 mg capsules. The study protocol was evaluated and approved by the Institutional Review Board (IRB # 05001) of Alluri Sitarama Raju Academy of Medical Sciences (ASRAM), Eluru, India. The IRB application also approved the use of antibiotic therapy as a rescue medication for the women subjects as deemed necessary by the investigators.

After randomization, three participants from the untreated control group dropped out of the study citing personal reasons. The study design is outlined in Fig. (1). Each woman completed a questionnaire providing demographic data, medical history, and nutritional status at the time of

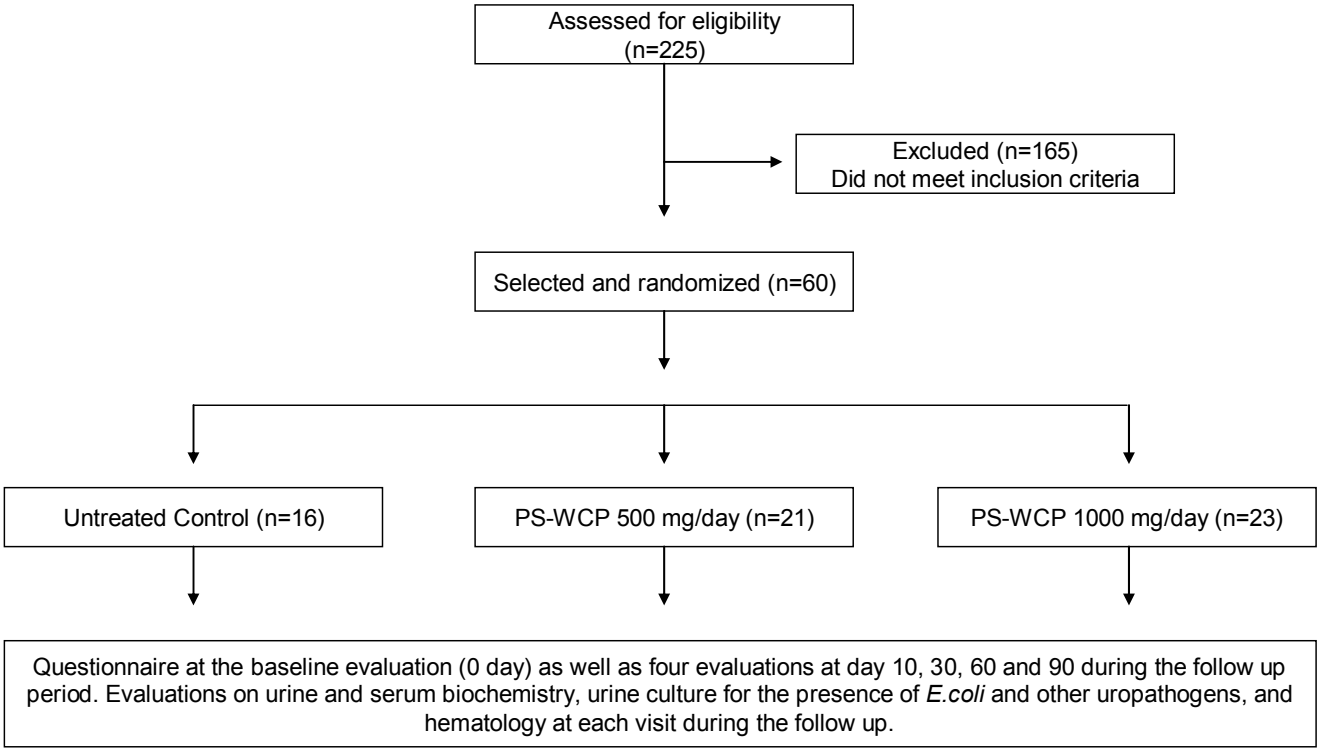


Fig. (1). Study design including recruitment of participants and strategy during the follow up.

baseline evaluation and during the follow up period at day 10, 30, 60 and 90. At the beginning of the study, patients were required to give written informed consent, they were instructed not to consume other *Vaccinium* products such as cranberries, blueberries, etc. and to report any adverse effects experienced at any time during the course of the study. At the base line evaluation, and at each visit during the 90 day period of follow up, all participants were assessed for symptoms of UTI, serum biochemistry, hematology, complete urinalysis and urine culture for presence of *E. coli* and other uropathogens (Table 2).

Each participant was instructed to collect their midstream urine in sterile containers and the samples were immediately processed for culture by standard procedure. Each urine sample was diluted to 10², 10³, and 10⁴-fold with sterile phosphate buffered saline, pH 7.2. Presence of lactose-fermenting bacteria was checked in MacConkey agar plates. Thereafter, uropathogens such as *E.coli*, *Klebsiella* spp. and *Enterobacter* spp. were confirmed in a chromogenic medium, Urichrom agar II [19]. Finally, the presence of *E.coli*, *Klebsiella* spp. and *Enterobacter* spp were individually identified biochemically by the IMViC (indole, methyl red, Voges-Proskauer, and citrate) test on TSI (triple sugar iron) agar slants [20]. Additionally, motility indole lysin (MIL), and nitrate reduction tests were conducted for further confirmation of *E. coli*. The bacteriological culture media were purchased from HiMedia Laboratories, Mumbai, India.

The confirmed pure growth of greater than or equal to 10⁴ colony-forming units per ml (cfu/ml) *E.coli* in urine samples from subjects (who also had symptoms consistent

Table 2. Biochemical and Hematological Parameters Evaluated at Each Visit During the Study

1. Hematology
Hemoglobin
WBC and differential count
ESR
Platelet count
2. Serum biochemistry
Fasting glucose
Triglycerides, cholesterol, bilirubin CK- NAC, SGOT, SGPT, Urea, creatinine
3. Urine analysis
Sugar
Albumin
Ketone bodies
Pus cells, RBC

ESR, erythrocyte sedimentation rate; CK -NAC Creatine kinase-n-acetyl cysteine ; SGOT, serum glutamic oxaloacetate transaminase SGPT, serum glutamate pyruvate transaminase; WBC, White blood count

with mild UTI), was selected as the criterion for the presence of UTI [21]. All the analyses were performed at ASRAM clinical laboratory, Eluru, India. The laboratory staff was unaware of the group assignment of participants and each

clinical observation was kept confidential throughout the study.

Statistical Analysis

We performed detailed statistical analyses to compare the efficacy of two doses of PS-WCP with the untreated control group in reducing the detection of urinary *E.coli*, with respect to the base line, and at 10, 30, 60 and 90 days after enrollment. We first performed an F-test on positive cases. We also performed multiple comparison tests using Tukey's test and Fisher's least significant differences. We further performed all possible pair-wise t-tests for the baseline and other time periods as described before. We scored for bacterial load for each subject and transformed it into a logarithmic scale and performed an ANOVA test. A time-series analysis was also performed to test the autocorrelation between bacterial loads.

RESULTS

Baseline Evaluations

A total of 225 participants were evaluated for this trial, and the major reasons for exclusion were age, history of hyperglycemia and in some cases, cardiovascular diseases. Although we did not record the sexual behavior of the participants, we included only sexually active subjects in the study. After screening, 60 participants were selected, randomized and distributed into three groups according to the study design (Fig. 1) with 16, 21 and 23 participants included in the untreated control, 500 mg/day and 1000 mg/day of PS-WCP treatment groups, respectively. Immediately after randomization however, three participants from the untreated control group declined to participate in the study. The overall characteristics of participants in all the groups were similar except the percentage of urinary *E. coli* positive cases at the baseline evaluation (Table 3).

Hematological and Biochemical Evaluations

Cranberry products have been considered safe for human consumption, although specific long-term safety data are not available. We have evaluated the hematological, and biochemical parameters in serum and urine samples collected from the low and high dose treated groups and compared them to the untreated control group. The list of the parameters tested is included in Table 2. Our detailed statistical analyses show that at the end of the 90-day follow-up period, no significant changes were observed in the hematological and serum biochemical parameters in the treatment groups. These observations suggest that the powdered cranberry product PS-WCP is safe and nontoxic for human consumption.

Overall Improvement of Symptoms and Reduction in Uropathogen Load in Treatment Groups

For the measurement of the overall improvement, a questionnaire-based assessment was performed. Eighteen participants out of 44 in the treatment groups stated that they had complete relief and remission from urological symptoms such as itching and burning sensation during micturition, and frequent urination. Subjects in both treatment groups reported significant improvement of symptoms starting from the 10-day evaluation compared to the baseline, while subjects in the untreated control group did not show any improvement in their symptoms. Both treatment groups also exhibited significant reduction of *E. coli* load (low dose, $p < 0.01$; high dose $p < 0.0001$; at a statistical significance level of 95%) after 10 days of treatment. At the end of the study (90 days), there was no significant change in the detection of *E. coli* in the urine of subjects in the untreated control group ($p = 0.7234$), when compared to the baseline (Figs. 2, 3). *E. coli* was reduced at highly significant level ($p < 0.0001$), and at a moderately significant ($p = 0.0151$) level in the high dose and low dose treated groups, respectively (Figs. 2, 3).

Table 3. Baseline Characteristics (n=57) of Three Individual Groups Included in the Study. The Figures in Parentheses Represent the Percentages, and were Calculated from the Numbers of Subjects in the Respective Groups

Baseline Evaluation

Parameters	Untreated Control (n=13)	PS-WCP	
		500 mg/day (n=21)	1000 mg/day (n=23)
1. Age (years)			
Mean +/- SD	32.8 +/-8.5	31.8 +/-8.4	30.9 +/- 10
Age 18-25	4 (30.76)	5 (23.8)	7 (30.43)
Age 26-34	3 (23.08)	11 (52.38)	8 (34.78)
Age 34-40	6 (46.15)	5 (23.8)	8 (34.78)
2. Urological symptoms Painful/burning micturition and lower abdominal pain	9 (69.23)	15 (71.42)	15 (65.22)
Urgency/frequency	4 (30.76)	6 (28.57)	8 (34.78)
3. Presence of urinary <i>E. coli</i>	4 (30.76)	14 (66.66)	17 (73.91)
4. Albuminuria	3 (23.08)	4 (19.04)	5 (21.73)

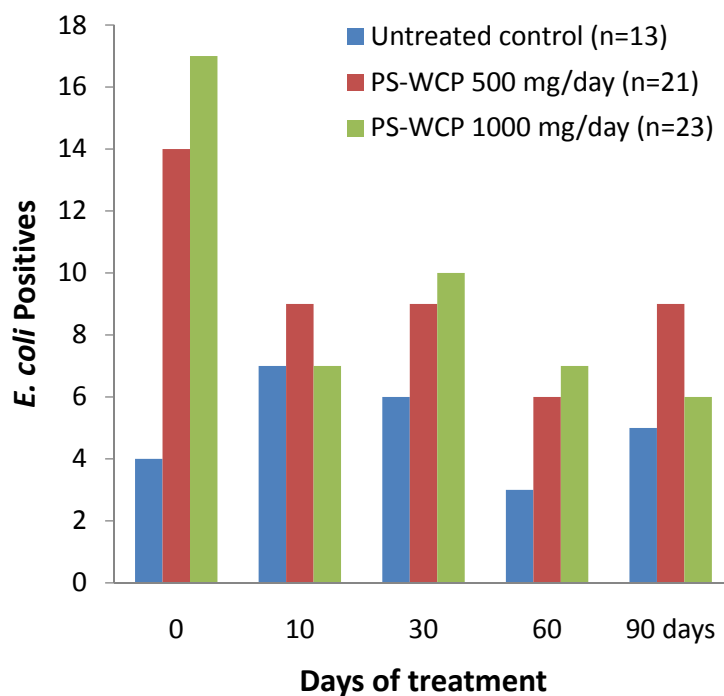


Fig. (2). Percentage urinary *E. coli* positive subjects in the control, 500 mg/day PS-WCP and 1000 mg/day PS-WCP at baseline and at 10, 30, 60 and 90 day evaluation.

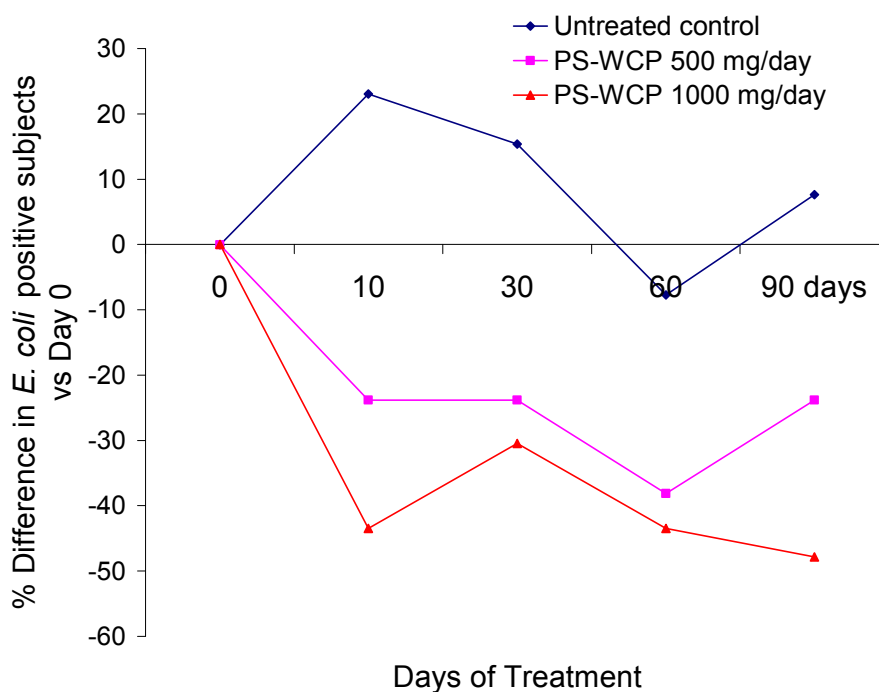


Fig. (3). Percentage difference in *E. coli* positive subjects in the control and treatment groups at 10, 30, 60 and 90 day evaluation vs. baseline evaluation.

This study showed no significant reduction of other uropathogens in the treated groups (Table 4).

Adverse Events

There were no serious adverse events during the study period. Very mild adverse events occurred during the study as detailed below, and no subjects withdrew from the study

due to adverse effects. General weakness and lower abdominal pain were recorded in three and one patients, respectively in the 500 mg/day and 1000 mg/day PS-WCP groups. A mild fever (99.5 °F to 100 °F) was reported by three participants in the 1000 mg PS-WCP group. Two participants in this group complained of heartburn at the 60th day visit during the study. Two participants in the untreated control group reported “stomach burn” and general weakness during the

Table 4. Presence of Urinary *E. coli* and Other Uropathogens in Different Groups at Baseline Evaluation and at the End of the Follow up Period of the Study. The Figures in Parentheses Represent the Percentages, and Were Calculated from the Numbers of Subjects in the Respective Groups

Group	Baseline (0 day)		90 Day	
	<i>E. coli</i>	Other uropathogens*	<i>E. coli</i>	Other uropathogens*
Untreated control (n=13)	4 (30.8)	11 (84.6)	5 (38.5)	12 (92.3)
PS-WCP 500 mg/day (n=21)	14 (66.7)	8 (38.1)	9 (42.8)	7 (33.3)
PS-WCP 1000 mg/day (n=23)	17 (74)	10 (43.5)	6 (26.1)	8 (34.8)

* Include *Klebsiella* spp, *Staphylococcus*, and *Enterobacter* spp

follow-up period. Overall, it was evident that this cranberry product was well accepted by all participants. Furthermore, supplementation of PS-WCP over a period of 90 days did not result in antibiotic resistance among the bacteria detected, which substantiates the safety of PS-WCP over prolonged use.

Use of Rescue Medication

During the clinical study, most of the subjects in the treatment groups indicated beneficial results and relief from the symptoms of UTI. During the entire period of this study, a total of 8 subjects reported severe complaints of UTI and were given 400 mg of norfloxacin twice a day for seven days. Out of these eight severe cases, four belonged to the untreated control group and two subjects were from each treatment group.

DISCUSSION

Results obtained from our present study confirm previous reports that symptomatic recurrences of UTI can be prevented by cranberry products. Urinary tract infections (UTIs) are common bacterial infections in women and >50% of women suffer from a UTI at least once in their life time [2]. At least one-third of the patients suffer from recurrences of UTI within the first year following an infection, and the risk increases with time [2]. *E. coli* is the most common pathogen, accounting for roughly 80% of infections, while *Staphylococcus saprophyticus* and other pathogenic bacteria including *Klebsiella*, *Enterobacter*, *Serratia*, and *Staphylococcus aureus* are responsible for the rest [3]. The first line of therapy for UTIs has been antibiotics including ciprofloxacin, ofloxacin, trimethoprim, and nitrofurantoin [22]. An appropriate alternative/adjunct therapy for recurrent UTI is most desirable because antibiotic treatment results in increase in resistance to antimicrobials among uropathogenic bacteria [23, 24], in addition to the potential side effects and high cost of the drugs [22]. A recent study compared cranberry extract to trimethoprim for the prevention of recurrent UTI and found that the latter had a very limited advantage and more adverse effects over cranberry extract [25]. In this randomized, clinical trial we have evaluated the safety and efficacy of a commercially available proanthocyanidin standardized powdered cranberry product, against recurrent UTIs in women.

Adherence of uropathogens to uroepithelial cells is the initial and key step in the pathogenesis of UTI [9, 24]. As far back as 1984, Sobota showed that cranberry juice has the ability to inhibit the adherence of *E. coli* to uroepithelial cells [26]. Cranberry juice cocktail reduced adherence by 75% in 60% of 77 clinical isolates of *E. coli* isolated from UTI patients and significant anti-adherence activity was observed in their urine after drinking 15 oz (443.6 ml) of cranberry juice cocktail [26]. A unique polymeric compound, proanthocyanidin (PAC), is the active ingredient present in cranberries which shows very strong inhibitory activity against mannose-resistant adhesins produced by urinary isolates of *E. coli*, and therefore, inhibits bacterial adherence to uroepithelial cells [9, 27]. The product tested in our study contains a high concentration of PACs with the type-A linkages that are attributed to be the active moieties responsible for the anti-adhesion effect against uropathogenic *E. coli* [6, 9].

In the past few years, a series of clinical studies have documented that cranberry juice provides a potential alternative to antibiotics in the prevention of recurrent UTIs [7, 8, 10, 13]. Although these studies showed significant reductions in the recurrence of UTI, the major criticism of these studies is high drop-out rates [9, 14]. The most likely reasons for the high drop-out rates might be the acidic taste which is unacceptable to most participants and high caloric load [9]. In this regard, the novelty of our study is that we have used a PS-WCP which is encapsulated 100% dried whole powder of Early Black cranberry which provides a high concentration of bioactive PACs (1.5% measured via HPLC) compared to other cranberry products. It allows a smaller capsule size to attain the same dosage as other products. Although no direct comparison was made to cranberry juice, in our trial, no subjects withdrew from the study during the follow up period due to any adverse effects. This indicates that the cranberry product used in the study was well accepted by all subjects in the study. Additionally, the capsules would be more cost-effective than cranberry juice [15], and did not result in antibiotic resistance in the uropathogens identified in study subjects.

As noted above, the major causative pathogenic organism in UTI is *E. coli*, accounting for approximately 80% cases [3]. We have evaluated the efficacy of a commercially available, PS-WCP by assessing the reduction in urinary *E. coli* during a 90-day follow-up period. In our study, we first performed a qualitative assessment for the confirmed presence

or absence of *E. coli* in the urine samples. After obtaining a characteristic colony growth from at least 10^4 -fold diluted urine in Urichrom Agar plates, the colonies were further confirmed as *E. coli* by the IMViC test, Motility indole lysin (MIL), and nitrate reduction tests. We considered the presence of a pure growth of *E. coli* at the 10^4 -fold diluted urine samples as the indication of UTI, which is comparable to previous studies where 10^4 cfu/ml *E. coli* was taken as the cut off limit for presence or absence of UTI [21], although other studies have used a 10^5 cfu/ml limit. We noted that at the end of the 90-day follow up period, there was a 36% and 65% reduction of urinary *E. coli* infection reported in the 500 and 1000 mg/day groups, respectively, even though there were no differences noted in the absolute number of positive cultures for *E. coli* in each of the three groups. Our study thus demonstrated a highly significant reduction ($P < 0.0001$) in urinary *E. coli* occurrence in the 1000 mg/day group when compared to the baseline. Whereas, change in the presence of *E. coli* at 90 days in the untreated control group was not significant when compared to baseline ($p = 0.7234$). It also indicates that the effect in the low dose and high dose groups was not significantly different, but both had significant reduction in urinary *E. coli* as well symptoms compared to the control group.

At the baseline evaluation, in lower and high dose treatment groups, 38.1% and 43.5% of the subjects respectively were found to be positive for uropathogens other than *E. coli*. At the end of follow up, these other uropathogenic loads were not significantly reduced to 33.3% and 34.8%, respectively (Table 4), indicating that the observed effect was likely due to the anti-adhesion effect of the PACs only against uropathogenic *E. coli*. By a different evaluation, out of 13 uninfected women in the treatment groups at day 0, nine remained uninfected with *E. coli* at 90 days. This indicates that in our study, PS-WCP was 69.2% effective in preventing *E. coli* infection. Thus, although we did not find a statistically significant difference in UTI between the treatment and control groups at any of the time points, perhaps due to the small sample size, over the 90-day period, there was significant reduction in *E. coli* load in the treated groups, while no such difference was noted in the control group.

Cranberry products appear to be a safe and herbal choice for UTI prophylaxis but specific safety data are still lacking. In our study we did not observe statistically significant differences in hematological and biochemical parameters in serum and urine samples of the treated groups when compared to the untreated control group. Our findings suggest that the powdered cranberry product PS-WCP is safe and well tolerated by the study subjects and no serious adverse events were recorded during the follow-up period. In addition, in an acute oral toxicity study conducted in female Sprague Dawley rats, the powdered cranberry product exhibited LD50 value of greater than 5g per kg body weight. Taken together, our observations strengthen the previous findings where cranberry products were supplemented up to 12 months, and found to be safe and moderately effective [15]. However, in a small study of 4 subjects, supplementation with cranberry concentrate tablets caused a significant rise in urinary oxalate which may increase the risk of nephrolithiasis [28]. Thus, appropriate care is necessary when

using cranberry products as supplements for patients with a history of oxalate calculi.

In summary, we report that a daily oral dose of a commercially available PS-WCP (500 mg or 1000 mg) has significant potential to prevent recurrent urinary tract infections in women and this product is non-toxic, safe and well tolerated by patients. Therefore, this cranberry product can be suggested as an alternative/adjunct measure to conventional antibiotic therapy for recurrent urinary tract infections in women. Antibiotics remain the first choice of treatment for UTIs, but data are emerging that cranberry products, particularly the extracts that are well-tolerated have a role in the prevention of recurrent UTIs.

REFERENCES

- [1] Foxman, B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. *Dis. Mon.*, **2003**, 49(2), 53-70.
- [2] Wagenlehner, F.M., Weidner, W., Naber, K.G. An update on uncomplicated urinary tract infections in women. *Curr. Opin. Urol.*, **2009**, 19(4), 368-374.
- [3] Ronald A. The etiology of urinary tract infection: traditional and emerging pathogens. *Dis. Mon.*, **2003**, 49, 71-82.
- [4] Wagenlehner, F.M., Pilatz, A., Naber, K.G., Perletti, G., Wagenlehner, C.M., Weidner, W. Anti-infective treatment of bacterial urinary tract infections. *Curr. Med. Chem.*, **2008**, 15(14), 1412-1427.
- [5] *The Cranberry Institute*. Available at: <http://www.cranberryinstitute.org>
- [6] Howell, A.B. Bioactive compounds in cranberries and their role in prevention of urinary tract infections. *Mol. Nutr. Food Res.*, **2007**, 51, 732-737.
- [7] Raz, R., Chazan, B., Dan, M. Cranberry juice and urinary tract infection. *Clin. Infect. Dis.*, **2004**, 38, 1413-1419.
- [8] Kontiokari, T., Salo, J., Eerola, E., Uhari, M. Cranberry juice and bacterial colonization in children—a placebo-controlled randomized trial. *Clin. Nutr.*, **2005**, 24, 1065-1072.
- [9] Guay, D.R. Cranberry and urinary tract infections. *Drugs*, **2009**, 69(7), 775-807.
- [10] Nowack, R., Schmitt, W. Cranberry juice for prophylaxis of urinary tract infections—conclusions from clinical experience and research. *Phytomedicine*, **2008**, 15(9), 653-67.
- [11] Pérez-López, F.R., Haya, J., Chedraui, P. *Vaccinium macrocarpon*: an interesting option for women with recurrent urinary tract infections and other health benefits. *J. Obstet. Gynaecol. Res.*, **2009**, 35(4), 630-639.
- [12] Bailey, D.T., Dalton, C., Joseph Daugherty, F., Tempesta, M.S. Can a concentrated extract prevent recurrent urinary tract infections in women? A pilot study. *Phytomedicine*, **2007**, 14(4), 237-241.
- [13] Kiel, R., Nashelsky, J., Robbins, B., Bondi, S. Does cranberry juice prevent or treat urinary tract infection? *J. Fam. Pract.*, **2003**, 52, 154-155.
- [14] Jepson, R.G., Craig, J.C. Cranberries for preventing urinary tract infections. *Cochrane Database Syst. Rev.*, **2008**, (1), CD001321.
- [15] Stothers, L. A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products against urinary tract infection in women. *Can. J. Urol.*, **2002**, 9, 1558-1562.
- [16] Vorsa, N., Howell, A.B., Foo, L.Y., Yinrong, L. Structure and genetic variation of cranberry proanthocyanidins that inhibit adherence of uropathogenic P-fimbriated *E. coli*. *ACS Symp. Ser.*, **2003**, Vol. 851, Chap. 26, pp. 298-311.
- [17] Prior, R.L., Lazarus, S.A., Cao, G., Muccitelli, H., Hammerstone, J.F. Identification of procyanidins and anthocyanins in blueberries and cranberries (*Vaccinium* Spp.) using high-performance liquid chromatography/mass spectrometry. *J. Agric. Food Chem.*, **2001**, 49, 1270-1276.
- [18] Gu, L., Kelm, M.A., Hammerstone, J.F., Beecher, G., Holden, J., Haytowitz, D., Prior, R.L. Screening of foods containing proanthocyanidins and their structural characterization using LC-MS/MS and thiolytic degradation. *J. Agric. Food Chem.*, **2003**, 51, 7513-7521.

- [19] Lakshmi, V., Satheeshkumar, T., Kulkarni, G. Utility of Urichrom II- A chromogenic medium for uropathogens. *Indian J. Med. Microbiol.*, **2004**, 22, 153-158.
- [20] Hitchins, A., Feng, P., Watkins, W., Rippey, S., Chandler, L. *Bacteriological Analytical Manual*, 8th ed., Revision A, Chap. 4. U.S. Food & Drug Administration Center for Food Safety & Applied Nutrition, **1998**.
- [21] McMurdo, M., Bissett, L., Price, R., Remy, J., Phillips, G., Crombie, I. Does ingestion of cranberry juice reduce symptomatic urinary tract infections in older people in hospital? A double-blind, placebo-controlled trial. *Age Ageing*, **2005**, 34, 256-261.
- [22] Anonymous. *Bacterial Infections: Urinary Tract Infections. The Merck Manual*, Sec. 17, Chap. 227, **2006**.
- [23] Chulain, M., Murray, A., Corbett-Feeney, G., Cormican, M. Antimicrobial resistance in *E.coli* associated with urinary tract infection in the west of Ireland. *Ir. J. Med. Sci.*, **2005**, 174, 6-9.
- [24] Arslan, H., Azap, O., Ergonul, O., Timurkaynak, F.; Urinary Tract Infection Study Group. Risk factors for ciprofloxacin resistance among *Escherichia coli* strains isolated from community-acquired urinary tract infections in Turkey. *J. Antimicrob. Chemother.*, **2005**, 56, 914-918.
- [25] McMurdo, M.E., Argo, I., Phillips, G., Daly, F., Davey, P. Cranberry or trimethoprim for the prevention of recurrent urinary tract infections? A randomized controlled trial in older women. *J. Antimicrob. Chemother.*, **2009**, 63(2), 389-395.
- [26] Sobota, A. Inhibition of bacterial adherence by cranberry juice: potential use for the treatment of urinary tract infections. *J. Urol.*, **1984**, 131, 1013-1016.
- [27] Pinzón-Arango, P.A., Liu, Y., Camesano, T.A. Role of cranberry on bacterial adhesion forces and implications for *Escherichia coli*-uroepithelial cell attachment. *J. Med. Food*, **2009**, 12(2), 259-270.
- [28] Terris, M., Issa, M., Tacker, J. Dietary supplementation with cranberry concentrate tablets may increase the risk of nephrolithiasis. *Urology* **2001**, 57, 26-29.

Received: March 2, 2010

Revised: July 20, 2010

Accepted: August 4, 2010