

# Cranberry for the Prevention and Treatment of Non-Complicated Urinary Tract Infections

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## Abstract

The increasing prevalence of resistance development of uropathogens to antibiotic treatment of urinary tract infections (UTI) has stimulated interest in naturopathies including use of cranberry. Cranberry (*Vaccinium macrocarpon*) ingestion, particularly in the form of cranberry juice, has long been associated with prevention and treatment of urinary tract infections. Cranberry has many chemical components which might possess beneficial properties in either preventing or treating non-complicated urinary tract infections. One group of chemicals in particular, proanthocyanidins (PACs) has shown the ability to inhibit the adhesion capacity of certain strains of *E. coli*, which are the primary bacteria associated with UTIs. Data collected and analyzed by this review provided contradicting results. Some studies showed potential benefit of using cranberry products to prevent or treat UTIs, while others showed the contrary. Most studies did not report the dose and dosage form used (tablets, capsules), optimum duration of treatment and amount of active ingredients in the cranberry products used.

**Keywords:** Cranberry; Urinary Tract Infections; Clinical Trials; Anti-Adhesion Activity; Procyanidine A2; Proanthocyanidines; A-Type Proanthocyanidine

## Introduction

Urinary tract infections (UTIs) are considered to be the most common bacterial infection. According to the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey in 1997, UTIs had accounted for nearly 7 million office visits and 1 million emergency department visits [1]. A more recent survey in 2007 indicated an estimated 10.5 million office visits for UTIs and 2-3 million emergency department visits in the United States [2]. With increasing numbers of UTIs, it is important to understand the causes, correct diagnosis, and appropriate medications to prevent and treat this infection. An accurate diagnosis requires the presence of signs and symptoms consistent with a UTI and a positive urine culture. Due to a lack of positive urine cultures being made before treatment of UTIs in the outpatient setting, it is difficult to assess the incidence of this bacterial infection.

The most common microorganism causing this infection is *Escherichia coli*. Other gram-negative microorganisms causing UTIs include *Proteus*, *Klebsiella*, *Citrobacter*, *Enterobacter*, and *Pseudomonas spp.* The three main gram-positive microorganisms that can also cause UTIs include *Enterococcus fecalis*,

*Staphylococcus saprophyticus*, and group B streptococci. Anaerobes may be present, but it is rare [2]. Although UTIs affect men and women, women are significantly more likely to experience UTIs compared to men. The ratio of women to men experiencing a UTI is 30:1 [3]. It is estimated that 1-in-3 women are diagnosed with a UTI by the age of 24 years. Among women who are diagnosed with cystitis, 25% will experience a recurrence within 6 months after the initial episode [4]. Recurring UTIs tend to involve the same microorganism from the first infection.

Treatment for UTIs per Infectious Diseases Society of America (IDSA) guidelines are divided between acute uncomplicated cystitis and acute pyelonephritis [5]. Acute uncomplicated cystitis mainly involves the bladder and is identified with signs and symptoms such as frequent urination, urgency, dysuria, burning upon urination, and possible gross hematuria or foul-smelling urine. Examples of antibiotics used for acute uncomplicated cystitis include Nitrofurantoin, Trimethoprim-sulfamethoxazole, Fosfomycin, Ciprofloxacin, and Augmentin (5). Acute pyelonephritis is a UTI originating in the kidneys. The signs and symptoms include cystitis symptoms plus signs of systemic infection. These symptoms may include flank pain, fever and/or chills, increased white blood cells, nausea and/or vomiting, suprapubic pain, and malaise. Some current treatment for acute pyelonephritis consists of Ciprofloxacin, Trimethoprim-sulfamethoxazole, and Ceftriaxone (5). With the use of antibiotics comes the increase in resistance and limitations for certain patient populations due to adverse effects. Trimethoprim-sulfamethoxazole is a widely prescribed antibiotic for the treatment of both types of UTI, but it is contraindicated in pregnancy. As for patients with heart diseases, fluoroquinolones (i.e. Ciprofloxacin and Levofloxacin) can prolong the QTc interval [6]. In these situations, patients may benefit from the use of a natural remedy instead. Natural products have been studied in several trials to demonstrate the safety, efficacy, and potential savings in treatment compared to antibiotics. It was estimated that the cost of healthcare in treatment of UTIs, including time missed from work, to be approximately \$3.5 billion per year in the United States (2). Due to UTIs affecting so many patients in terms of quality of life, hospital stays, healthcare costs and loss of productivity, it is important to recognize natural products that may prevent or treat signs and symptoms of this infection.

The cranberry species is diverse and includes both the American species, and the European species. Recently, studies have identified the chemical composition of cranberries and several components have been isolated and recognized in various fractions figure 1.



Figure 1: *Vaccinium microcarpon*

The purpose of this review is to examine if cranberry products are an appropriate natural alternative for the prevention and treatment of UTIs with consideration of drug formulation, dosing, safety and efficacy. Data were collected by searching the PubMed database, internet and Google scholar with the keywords "cranberry in UTI", "cranberry prophylaxis", "cranberry antibacterial", "and cranberry components", "UTI epidemiology", "proanthocyanidin", "procyanidin A2".

## Constituents of cranberry

Among the chemicals isolated, the following have been identified as the major constituents of cranberry: anthocyanins, flavonols and PACs (proanthocyanidins), flavan-3-ols, phenolic acid derivatives, and triterpenoid analogues [7, 8, 9]. Several catechin derivatives have been reported to exist in cranberries [7, 10-12]. Proanthocyanidins are a class of polyphenols found in a variety of plants. Chemically they are oligomeric flavonoids. Many are oligomers of catechin and epicatechin (figure 2) and their gallic acid esters which are often associated with consumer products made from cranberries, grape seeds or red wine. Multiple sterols, iridoid glycosides, and other terpene derivatives have been isolated from whole cranberry fruit [7, 13]. The cell wall composition of the cranberry includes multiple complex carbohydrates like pectin, cellulose, and hemicelluloses [5, 26]. An assortment of sugars like sucrose, glucose, fructose, and sorbitol has been detected within cranberry fruit. Also, a wide variety of vitamins and provitamins have been identified including Vitamin C (23%) [7, 9, and 14]. Cranberry's chemical composition can be depicted as 39.4% sugars (glucose and fructose), 30% organic acids (malic, citric, shikimic and quinic acids with predominant being quinic acid), 10.6% polyphenols, 5.5% proanthocyanidins, and 1.2% anthocyanins [15]. Citric and malic acids are used as food preservatives and are known to inhibit a wide variety of microorganisms [16].

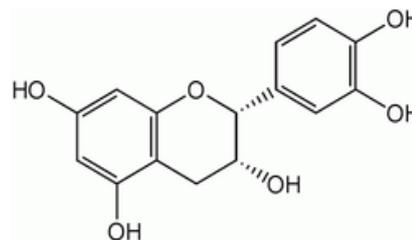
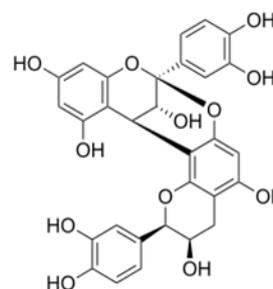


Figure 2: Epicatechin, one of the building blocks of proanthocyanidins



Procyanidine A2 is A -type proanthocyanidine, a dimeric catechin found in cranberry, avocado, and chest nut. Proanthocyanidine content in cranberry samples is estimated by a spectrophotometric method using 4-dimethylaminobenzaldehyde and procyanidin A2 as standard that is commercially available [16]. Howell A.B et al compared the in-vitro antiadhesion activity of A-linked proanthocyanidines from cranberry juice cocktail and B-linked proanthocyanidines from grape and apple juice, green tea and dark chocolate and found that the A type elicited in-vitro anti-adhesion activity at 60 microgram/ml while the B-type from grapes exhibited low activity at 1200microgram/ml and some other B-type were not active at all [17].

An HPLC method also has been reported for the determination of proanthocyanidin A2 [18].

## Mechanism of action

Studies dating back to the early 1900s describe the possible mechanism of action to be the reduction of urine pH brought about by the high phenolic contents and organic acids in cranberry extracts. However, further studies have shown that the more acidic urine does not really create a bacteriostatic environment [7, 19]. Furthermore, a large quantity of either cranberry fruit or cranberry juice is required to even slightly lower the urine pH [7, 19]. Another proposed mechanism of action is the bacterial adherence to mucosal surfaces, which is generally an important factor for colonization leading to infection. There have been numerous investigations focusing on the anti-adhesion effects that cranberries have on certain urinary bacteria [7, 20, and 21]. These studies indicated that cranberry juice could reduce the adherence of *E. coli* originating from patients with a confirmed UTI. Additionally,

studies later confirmed the link between cranberry anti-adherent properties and its efficacy in preventing UTIs [21]. The anti-biofilm property is also shown for *Pseudomonas aeruginosa* suggesting that cranberry may be useful for infections caused by this organism and *Candida albicans* biofilms in artificial urine [22]. There is only a limited data available regarding the use of cranberry in prevention and treatment of *Candida albicans* urinary tract infections [23]. Another proposed mechanism of action of cranberry is the non-enzymatic production of nitric oxide under acidic conditions. Nitric oxide can become activated via bacterial nitrate reductase and the induction of inflammation-driven nitric oxide synthase. This in turn could potentially create a bacteriostatic environment within the urinary tract [7].

### Clinical Trials

A double-blind randomized clinical trial, conducted by Genao L et al. 2011 [25] examined the efficacy of cranberry extract versus trimethoprim-sulfamethoxazole (TMP-SMX) in women over the age of 18 who had greater than 3 symptomatic UTIs within the past year. Exclusion criteria included contraindications to any of the study drugs, pregnancy, renal transplant, interactions with existing medications, and unresolved UTI. Inclusion criteria were women over the age of 18 and 3 or more UTIs during the past year. The intervention group of this trial included: 480 mg of TMP-SMX at night plus 1 placebo capsule twice daily or 500 mg of cranberry extract twice daily plus 1 placebo capsule at night. The investigators, health care providers, and patients were all blinded during the treatment. The primary endpoints were: incidence of UTI per year, proportion of subjects with greater than 1 UTI while on prophylaxis treatment, and time to first UTI. Secondary endpoints include: incidence of microbiological recurrence, greater than 1 microbiological recurrence while on prophylaxis, time to first microbiological recurrence within 12 months, culture susceptibilities, and drug adverse events.

Data collection was performed via questionnaires and urine samples sent by the mail. The dropout rate was around 53% for the cranberry group and 48% for the TMP-SMX group at 12 months. All patients that received at least 1 dose of either the intervention medication of cranberry extract or TMP-SMX were included in the final data analysis. The incidence of UTI per year was 0.8-2.7 for the TMP-SMX group and 2.3-5.6 for the cranberry extract group. After the study drugs were stopped, there were a similar proportion of subjects with at least 1 or greater confirmed UTI. Adverse effects of the study medications were similar, except TMP-SMX had significantly higher incidence of bacterial resistance compared to cranberry (91% vs. 28%). The authors of this study concluded that cranberry extract was non-inferior to TMP-SMX at reducing recurrent UTI in pre- and postmenopausal women. The authors also noted that there was a great deal of bacterial resistance within the TMP-SMX group.

A randomized, placebo-controlled study assessing the effectiveness of cranberry extract, specifically proanthocyanidin-A (PAC-A), on *E. coli* and its tolerability in patients with uncomplicated recurrent UTIs was reported by Singh et al [21]. Recurrent UTI was defined as 3 or more episodes in 1 year or 2 episodes within 6

months. In this study, 72 patients were randomly assigned to take cranberry extract or placebo over duration of two years. Patients with asymptomatic bacteriuria and/or recurrent UTI, those who were resistant to antibiotics and those at higher risk of developing a new or recurrent UTI were eligible for the study. In the treatment group, patients received a CranPac capsule, containing PAC-A 60 mg twice daily for 12 weeks. Patients in the controlled group received 1 capsule twice daily containing 400 million lactobacillus for duration of 12 weeks. Efficacy, tolerability, adverse reactions, and compliance were assessed with each patient. The primary endpoint measured was patient's well-being, urine routine, pH and culture, and recurrent rate after intervention. The study met power even after compensating the 20% loss or drop-out rate during follow-up. All baseline values such as age, urinary pH, score for dysuria and pyuria, bacterial adhesion and growth, biofilm, and MRHA (mannose-resistant hem-agglutination assay) were similar between intervention and placebo.

There was a significant decrease in bacterial adhesion, biofilm, and number of patients with bacterial growth in the intervention group. The results showed 33% patients developed a recurrent UTI in the cranberry group compared to 89% patients who developed a recurrent UTI in the placebo group ( $p=0.001$ ). The authors of this study speculated that PAC-A was significantly effective in reducing the recurrence of UTIs. Overall, cranberry extract was both tolerable and efficacious compared to placebo in reducing bacterial adhesion, urine pH, UTI recurrence, and amount of MRHA. In conclusion, this study supported the utilization of cranberry extract as prophylaxis against recurrence of non-complicated UTIs in select patients.

A review by Vasileiou I, et al. in 2007 (7) aimed to assess the fundamental mechanism of action of cranberries against UTIs. It also condensed results from current clinical literature for the efficacy of using cranberry in the possible treatment and prevention of UTIs in different populations. Many clinical trials were reviewed and cited in this article such as trials involving sexually active women with previous diagnosed UTI, elderly patients, pediatric patients, and patients with medical conditions predisposing to UTIs. All trials included were to evaluate whether or not cranberry products can manage UTIs, prevent the development of UTIs, or reduce the number of UTI recurrences. The results examined by this review were inconclusive due to many factors such as short trial length, missing dosing regimen, small trial populations, limited external validity, and inability to meet power. The reviewer's conclusion indicates the possibility of using cranberry products as an alternative to antibiotics in preventing recurrent UTIs seemed promising. However, based on the studies reviewed, an absolute conclusion cannot be drawn due to many study limitations.

A randomized, double-blind, placebo-controlled trial by Betsy Foxman, et al. [22] was the first in which cranberry juice capsules were tested in preventing UTIs in women who have undergone elective gynecological surgery in which a catheter was placed. At a single hospital from August 2011 through January 2013, one hundred sixty patients were randomized and either received 2 cranberry juice capsules 2 times a day for 6 weeks after surgery or placebo. Inclusion criteria included: be non-pregnant, at least 18

years of age, no history of nephrolithiasis, no congenital urogenital anomaly or neurogenic bladder, no known allergy to cranberry, no requirement for anticoagulation medication during the 6 weeks post operation, and no involvement of a fistula repair or a vaginal mesh removal. Treatment groups were balanced by age (<60 years old vs. ≥60 years old) due to increasing prevalence of bacteriuria with age. "The primary endpoint was the proportion of participants who experienced clinically diagnosed and treated UTI whether or not results from a urine culture were available. Secondary endpoints included the incidence of UTI caused by *E. coli* and time from randomization to UTI." The study procedure required all participants to complete a questionnaire regarding their medical and sexual history, health behaviors, and symptoms. A urine sample was collected at the time of admission, upon catheter insertion in the operating room and catheter removal. Participants in the cranberry group were instructed to take 2 cranberry juice capsules 2 times a day starting at the time of discharge for 4 to 6 weeks or until their postoperative visit. Participants were to collect a urine sample if urinary symptoms consistent with a UTI presented. Study staff followed up with participants within 3 days, and at 2 and 4 weeks after hospital discharge to ensure compliance and inquire about any UTI symptoms or adverse events. Of the 80 participants allocated to the cranberry group, only 74 patients received the intervention. Likewise, of the 80 participants allocated to the placebo group, only 76 patients received the intervention. A total of 10 participants did not receive the intervention due to one of the following reasons: no staff available to provide intervention at discharges, participant could not swallow the capsules or returned the bottle unopened, participant lost the capsules, instructions to avoid cranberry per the participant's physician, the surgery was cancelled, or the participant withdrew. Upon completion of this trial, the use of cranberry showed the ability to possibly lower the incidence of UTIs compared to the placebo group. Furthermore, the median time to UTI was significantly longer in the cranberry group compared to the placebo group. While some strengths of this study included randomization and double-blinding, this study is only applicable to women who have undergone an elective surgery requiring a catheter be placed and the study sample originated only from one hospital. Of note, the study needed at least 200 participants to meet 80% power with a 2-sided type I error of 5%. However, the sample size was limited to 150 participants due to budgetary and timing restraints. In conclusion, this study showed a possible clinical benefit when using cranberry juice capsules in the prevention of UTIs post elective gynecological surgeries in which catheterization was used.

A systematic review by Ângelo Luís, et al. 2017 [23] was performed as a meta-analysis and sequential analysis of clinical trials to compile a cohesive report on the efficacy of using cranberries in reducing the incidence of UTIs. This systematic review was conducted in September 2016 using various electronic databases. In compliance to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) statement, only the literature that was considered relevant after screening was used. Two researchers independently performed the literature search, with a third researcher to settle any disagreements. The risk of bias was assessed for each randomized controlled trial using the

Cochrane Library Tool. The sources of bias included the following categories: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The risk was categorized as low risk of bias, unclear risk of bias, or high risk of bias. Two researchers compiled this data with any discrepancies being resolved after further discussion. To analyze the data collected, a forest plot was produced to show study specific ratio risk and the weighted ratio risk estimate along with the 95% confidence intervals using the random effects model. The measure of inconsistency with the studies was reflected with the I<sup>2</sup> statistic. Three other analyses were performed to determine the potential impact of publication bias. These analyses included a funnel plot, Egger regression test, and the trim and fill approach. A sensitivity analysis was conducted by removing 1 study at a time to determine the change in results and the stability of the overall findings of this review. One hundred and thirty eight studies were screened and after assessing for eligibility, only 25 studies were included in this systematic review. Three of the 25 studies were divided into 2 trials rendering a total of 28 studies with 4,947 patients. Based on the findings and from this meta-analysis, the use of cranberry products in the prevention of UTIs demonstrated efficacy. There was strong evidence that cranberry can decrease the number of UTIs, especially in patients with recurrent UTIs. A subgroup analysis was conducted to determine if the findings were gender dependent since UTIs are more common in women. The result of the subgroup analysis indicated a significant decrease in UTIs in both men and women. Another subgroup analysis was performed to observe increased cranberry use with age given a UTI diagnosis. The result of this analysis indicated children 2 to 17 years old and adults aged 26 to 55 years old had a significant decrease in the incidence of UTIs. A final subgroup analysis was used to assess the effects of cranberry products among various patient types. This analysis concluded that individuals who had undergone gynecologic surgery experienced more protection by cranberry ingestion and demonstrated a significant reduction in the occurrence of UTIs. However, the findings from this meta-analysis did not provide evidence on the efficacy of cranberry products for chronic use. Furthermore, this systematic review did not assess the effectiveness of cranberry ingestion based on the concentration of proanthocyanidin found in the product. In conclusion, this systematic review with meta-analysis supported the recommendation of cranberry ingestion to decrease the incidence of UTIs, particularly recurrent UTIs.

A prospective, open controlled clinical trial, with a randomized distribution of participants was conducted from December 2012 to September 2013 by O.S. Barnoiu, et al. 2015 [24]. The study compared the UTI rate of patients carrying a double-J stent with prophylactic treatment with cranberry extract, 120 mg per day, versus patients with a double-J stent with the usual prophylactic treatment (sulfonamide, beta lactam, or quinolone). This trial had 31 patients in the treatment group and 31 patients in the control group. Exclusion criteria included: patients with a renal transplant, those who had undergone reconstructive surgery using bowel tissue, those who had a UTI prior to surgery and those carrying any other kind of catheter at discharge, such as a bladder catheter

or nephrostomy. Every patient was tested to ensure no urine dipstick resulted in positive nitrites before urethral catheter insertion. Prophylaxis started at the time of hospital discharge post inpatient surgery for extracorporeal lithotripsy, and a day before and up to 3 days after double-J stent placement. A third-generation cephalosporin plus an aminoglycoside was used in all cases as intraoperative prophylaxis in the event of a previous presence of a urinary catheter. A bivariate analysis revealed positive results were higher with a longer duration of catheterization ( $p=0.03$ ). Prophylaxis with cranberry demonstrated less positive results when compared to the control group ( $p=0.04$ ). A logistic model was then used to conclude that the effect of cranberry treatment reduced the risk of getting a positive result by five times compared to those in the control group. Also, women had a four times higher risk of getting a positive result compared to men. In conclusion, this study recommends a daily dosage of 120mg cranberry extract as adjuvant therapy for UTI prevention in patients with a double-J ureteral stent post-surgery. The first version of this review was published in 1998 and it has since been updated in 2004, 2008, and 2012. This 2012 update [25] was conducted by searching within the Cochrane Renal Group's Specialized Register. The search criteria consisted of all randomized controlled trials or quasi-randomized controlled trials of cranberry products for the prevention of UTIs. Two researchers independently assessed the data and calculated the risk ratio when appropriate. The Cochrane risk of bias assessment tool was used to determine the quality of the studies and potential bias. A total of 24 studies with 4,473 participants were analyzed. Studies that compared cranberry use with placebo, water or no treatment showed no significant reduction in the occurrence of symptomatic UTI. When the efficacy of cranberry is compared with antibiotics, there was no significant difference. There was no significant difference in adverse effects, specifically gastrointestinal issues between cranberry products and placebo/no treatment. Some common limitations found were low compliance and high withdrawal/dropout rates due to palatability of the cranberry products. Furthermore, most studies did not report how much of the active ingredient were in the cranberry products.

Based on previous trials testing the efficacy of cranberry products with a time frame of 12 months, results appeared to have some evidence of benefit in the incidence of UTIs. However, the addition of 14 further studies indicated cranberry was less effective and therefore cannot be recommended for prevention of UTIs.

A pilot study by Francesco Montorsi, et al. 2016 [26] looked at the effectiveness of cranberries in combination with *Lactobacillus rhamnosus* and Vitamin C for the management of recurrent UTIs in women. This study was conducted to further build upon previous research collected by the authors indicating that cranberries alone did not have significant effects in the majority of cases. Patients were selected based on the following inclusion criteria: 18 years of age or older, premenopausal and postmenopausal women,  $\geq 3$  episodes of UTIs with documented positive urine culture in the last 12 months, and normal abdominal ultrasonography. The exclusion criteria were as follows: immune compromising diseases, chronic

inflammatory bowel disease, uncontrolled diabetes, and known allergy to the nutritional supplements used in this study. All 42 patients within the study were examined by the same physician. Initially, patients with  $\geq 103$  colony forming units/mL were considered microbiologically diagnostic. After initial diagnosis, patients were treated by either empiric or targeted antibiotics. When the patients did not show significant benefit from the antibiotic treatments; they were interviewed to assess both maturation and sexual symptoms (dysuria, urgency, frequency, urinary incontinence, bladder tenderness, and pain). Patients that failed antibiotic therapy and proved to be candidates for cranberry therapy were treated with 120 mg of cranberry powdered extract, 1 billion heat-killed *Lactobacillus rhamnosus*, and 750 mg of Vitamin C taken orally 3 times daily for 20 consecutive days. After day 20, patients were advised to stop supplementation for 10 days. This made the administration cycle a total of 30 days. Along with the treatment cycle, patients within the study were advised to undertake lifestyle modifications. These modifications include increased water intake, good hygiene practices, increased physical activity, and decreased caffeine/alcohol intake.

The primary outcome of this study was a negative urinalyses/urine culture, as well as the absence of any symptoms associated with a UTI. A midstream urine catch method was employed to collect urine from test patients. If patients had  $\geq 103$  colony forming units/mL, then the supplemental treatment regimen was considered ineffective. Of the 42 patients enrolled in the study, 3 patients stopped treatment due to adverse effects, and another 2 patients were unreachable. These 5 patients were not considered to have completed the cohort. 38 patients completed the 3 cycles of treatment and were chosen for analysis. Patients were then followed up at 3 months and 6 months after treatment completion. At the 3-month checkup, only 36 patients were able to be reached. Of the 36 patients, 10 patients complained of recurrent symptoms associated with a UTI; and of these reports, eight patients tested positive for a UTI. Follow-up at 6 months included only 26 patients. 4 of the 26 patients complained of urinary symptoms with 3 reports leading to a positive UTI diagnosis. Overall, 26 patients responded positively to therapy at 3 months and 22 patients responded positively to therapy at 6 months. No major safety issues presented in any of the patients that completed the study. Based on data collected by this pilot study, the combination of 120 mg of cranberry powdered extract, 1 billion *Lactobacillus rhamnosus*, and 750 mg of Vitamin C taken orally 3 times daily seemed to be both safe and effective. This combination appeared to have superior efficacy than any single agent alone in the prevention of recurrent UTIs.

A review by Haim Shmueli, et al. 2012 [27] looked at the anti-adhesion properties associated with cranberry use and its effects on bacteria commonly linked to UTIs. These studies focused on certain bacteria affected by cranberry supplementation. Cranberry was shown to inhibit the adhesion of P-fimbriated uropathogenic *E. coli*, which is the most common bacteria associated with UTIs. Within these studies, multiple dosage forms were used and included both tablet and juice formulations. Results of these studies examining anti-adhesion qualities associated with cranberry supplementation showed 3 main conclusions: One conclusion was

that cranberry juice displayed the ability to inhibit hemagglutination and uroepithelial adhesion of P-fimbriated uropathogenic *E. coli*. Another conclusion indicated chemical components found within cranberries have been linked to the inhibition of adhesion between hem agglutination of uropathogenic *E. coli*. Lastly, uropathogenic *E. coli* collected from both humans and rodents that consumed cranberries exhibited anti adhesion activity. These studies provided evidence that the use of cranberry products could potentially offer prophylactic benefits for recurrent UTIs in women. The study also had an estimated withdrawal rate of around 55%, which could suggest either adverse events or adherence issues caused by an unknown reason. An interesting observation was the mixed efficacy in college-aged females; however, the cause was not confirmed. It was hypothesized that increased sexual activity of this age group or low-calorie formulations of cranberry juice containing sucralose as opposed to fructose were to blame. The authors concluded that current cranberry constituents are the only supplements provided over-the-counter and proven to be possibly effective for the control of UTIs.

A randomized clinical trial by Juthani-Mehta M, et al. 2016 [28] conducted from August 2012 to October 2015 aimed to determine the effectiveness of oral cranberry capsules used once daily in the presence of bacteriuria plus pyuria among women living in nursing homes. This study was double-blinded, randomized, intent-to-treat, two-sided alpha, placebo-controlled trial with stratification and surveillance of 1 year by the nursing home. One hundred and eighty five nursing home residents participated in the trial. All participants were at least 65 years old with or without bacteriuria and pyuria at baseline. An 80% power was calculated based on a sample size of 180 participants, which the study was able to meet. The primary outcome was the presence of bacteriuria plus pyuria which was assessed every 2 months for a total of 6 assessments over a 1 year surveillance period. If a positive result was detected, then the primary outcome was met. Secondary outcomes included symptomatic UTI, all-cause death, hospitalization by any cause, multi-drug resistant organisms, and antibiotics used to treat UTIs. Intervention included 2 oral cranberry capsules with each capsule containing 36 mg of the active ingredient proanthocyanidin, versus placebo administered once per day. There were 92 participants in the treatment group and 93 participants in the control group. Among the 185 women that participated within this trial, only 147 participants completed the study. Adherence to cranberry capsule administration was 80.1%. 25.5% of the patients within the treatment group experienced both bacteriuria and pyuria compared to 29.5% in the control group at 1 year ( $p=0.984$ ). No significant differences were detected regarding symptomatic UTIs, rates of death, hospitalization, multi-drug resistant gram-negative bacilli, or antibiotics administered for suspected UTI between the treatment and control groups. Based on the results of this clinical trial, there appeared to be no significant difference between the administrations of cranberry capsules versus placebo for nursing home residents being prophylactically treated for bacteriuria plus pyuria over 1 year.

A recent study by William Simonson, et al. 2017 [29] looked at the possible use of cranberry products in patients experiencing

a UTI. The author highlighted that PACs have been shown to alter certain strands of *E. coli*, thus making the bacteria less able to adhere to cells that line the urinary tract. Since *E. coli* was less likely to adhere, there was a decreased chance for colonization leading to infection. The authors noted that previous studies examining the efficacy of cranberries for the reduction of UTI occurrence had contradicting data. Some studies had indicated that recurrent UTIs in sexually active women can be reduced by up to 50%, while other studies had demonstrated no difference between cranberry supplementation compared to placebo. Complications also hindered a large majority of studies such as a high dropout rate, intolerance, and low compliance rate (usually occurring in juice dosage form). Lastly the author reviewed two studies that took place in the past 4 years. The first study which was published in 2017 compared the efficacy of 240 mL of a cranberry-containing beverage per day with the same amount of placebo in women with a recent history of UTI. After 24 weeks there was a 39% reduction in UTI occurrence for the patients using the cranberry-containing beverage. Another study analyzed the efficacy of cranberry supplementation in women over the age of 65 with an indwelling catheter. This study showed no reduction in incidence of bacteriuria. The authors closing statement emphasized further research on cranberry products for preventing recurrent UTIs. If further research can show cranberry products are effective at either the prevention or possible treatment of UTIs, then these products may become reasonable alternatives to antibiotic therapy.

Two studies [30, 31] using standardized cranberry extract, Anthocran, as prophylaxis for recurrent urinary tract infections were reported in 2016 and 2017. Both studies were performed over 2-month duration. The first study targeted young, healthy subjects between the age of 12 and 18 with a previous history of recurrent UTIs. A total of 36 participants were enrolled in the study with 17 and 19 participants receiving standard management and standard management plus cranberry supplements, respectively. Standard management includes hygiene and lifestyle interventions. These include having access to clean toilets when needed, drinking and voiding at a certain time, appropriate washing, and treating constipation if experienced. Oral cranberry supplementations have 120 mg of Anthocran in one capsule, equivalent to 36 mg PACs used in most studies for the prophylaxis and treatment of UTI in subpopulations. Both of the groups had similar baseline characteristics such as age, gender distribution, number of UTIs before inclusion, and the days of follow-up. The mean numbers of UTIs observed were lower in the supplemented group versus the controlled group. Furthermore, there was a statistically significant difference in the number of participants experiencing symptoms of UTIs with  $p$ -value  $< 0.05$ . About 63% of participants in the supplementation group were symptom-free compared to 24% in the control group.

The second study focused on the prevention of recurrent urinary tract infections in elderly men suffering from moderate prostatic hyperplasia. Methods and duration of intervention were similar to the first pilot study. A total of 43 men over the age of 65 were enrolled in this study. In the intervention group, the mean number of UTI events during the registry was  $0.8 \pm 0.5$  compared

to control group at  $3.2 \pm 1.3$ . With a p-value = 0.0062, the authors concluded that oral cranberry supplements in the intervention group were more superior in the standard management of UTIs. Both of these studies provided compelling evidence that using cranberry extracts as prophylaxis is safe and effective against recurrent UTIs.

A study by Jensen, et al. 2017 [32] used an experimental mouse model to evaluate the effectiveness of cranberry juice and combinations of its organic acids against experimental UTIs. This was the first study to show that cranberry juice lowers *E. coli* colonization of the bladder in an experimental mouse model of UTI. In this study, *E. coli* were grown overnight at 37°C and were injected into the bladder of female mice 6 to 8 weeks old. These mice were then inoculated and sacrificed after 7 days. The control and treatment groups consisted of 6 mice each. After inoculation, drinking water was substituted with cranberry juice bioactive compounds in water for the remainder of the experiment. The experiment was repeated at least twice for accuracy. The results demonstrated that commercially available and fresh cranberry juice significantly reduced bacterial counts in infected bladders. Furthermore, a combination of the most prevalent organic acids in cranberries has an effect against bladder infection. Results also showed that mice treated with cranberry juice or solutions of organic acids had lower fluid intake and lower urinary pH. Treatment of mice with infected bladders utilizing commercial cranberry juice cocktail reduces bacterial counts by 65% and 47% with fresh cranberry juice. The P-value was less than 0.01. Organic components of cranberry juice including citric-, malic-, quinic (a cyclic polyol) - and shikimic acids (a cyclohexane carboxylic acid) were tested in amounts equivalent to fresh cranberry juice concentrations. A cocktail with all four organic acids decreased bladder infection by 52% with p-value <0.001. Similarly, treatment with malic-/citric- and malic-/quinic- decreased infection by 47% and 81% with p-value < 0.01 and p-value <0.05, respectively. Treatment with other combinations did not have any effect against bladder infection. Mice were also treated with a low pH fluid buffer including phosphate to obtain a pH of 3. The treatment of oral administration of low pH fluid did not impact bacterial counts in mice with infected bladders. Lastly, this experiment showed that mice given either cranberry juice or organic acid solutions in place of water consumed a smaller amount of water compared to the control group. This could be due to mice in the control group drinking more as a result of having an active infection. Another explanation could be due to the sour taste of cranberry juice or its acidic contents causing mice in the treatment group to drink less. Overall, this study supported the antibacterial effects of cranberry juice consumption and utilizing mixtures of organic acids to reduce bacterial count in the bladder.

In a study by Afshar K et al [38] 40 children were randomized to receive daily cranberry juice with high concentration of proanthocyanidin vs. cranberry juice with no proanthocyanidine for a one year; the authors found a 65% reduction in the risk of urinary tract infection. In a similar study in Finland, 255 children were randomized to receive either cranberry juice (n=129) or placebo (n=134) for 6 months and recurrent UTI were recorded for

one year [39]. Commercially available cranberry juice containing 41grams of cranberry concentrate in one liter of juice was used in the treatment group. 16% children in the cranberry group and 22% in the placebo group had at least one recurrent UTI and children in the cranberry group had significantly fewer days on antimicrobials.

### Conclusion

The existing clinical trials suggest that the beneficial effects of cranberry against UTIs seem to be prophylactic by preventing development of infections. They also have low effectiveness in populations at increased risk for contracting UTIs. The composition of cranberry products used in clinical trials and its dosage in UTI prophylactics has not been well-defined. However, evidence is available regarding the antiadhesive mechanism of cranberry juice that prevents adhesion of bacteria on uroepithelial cells and thus decrease the incidence of UTIs without adverse effects in most patients. Proanthocyanidins with an A type linkage of flavones seems to be responsible for this antiadhesive property but little is known about the bioavailability and their structure-activity relationship. Since the American cranberry (*Vaccinium macrocarpon*) and European cranberry (*Vaccinium oxycoccus*) have different pattern of type A proanthocyanidines, caution is required in extrapolating results from one species to another. In the present review, five of the 12 studies advised against the use of cranberry products for prophylaxis or treatment of non-complicated UTIs. In most situations, the cranberry product being tested did not show superiority to a placebo in the patients enrolled within these trials. The remaining 7 sources examined in this review acknowledged the possible beneficial use of cranberry products for prophylaxis or treatment of non-complicated UTI. Based on the information examined in this review, more in-depth research is required with standardized cranberry products before recommending them for the prophylaxis or treatment of non-complicated UTIs. Evidence suggesting that cranberries may decrease the recurrence of urinary tract infections is important because a nutritional approach to this condition could lower the use of antibiotic treatment and the consequent development of resistance to these drugs.

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