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Cranberry juice vs. placebo as prophylaxis for recurrent urinary tract infection in adult women: A systematic review

Donald S. Trawick
James Madison University

Hinda Mezaache
James Madison University

Cranberry Juice vs. Placebo as Prophylaxis for Recurrent Urinary Tract Infection in Adult Women

A Systematic Review

Hinda Mezaache, PA-S and Scott Trawick, PA-S

ABSTRACT

Objective: To determine the effectiveness of cranberry juice consumption as prophylaxis for urinary tract infection (UTI) in women with a history of recurrent UTI. **Methods:** Systematic literature review using Google Scholar with search terms "cranberry juice prophylaxis." **Results**: Our search resulted in three randomized-control trials (RCTs), two of which demonstrated no benefit of cranberry juice in preventing recurrent UTI. **Conclusion:** Because of the significant heterogeneity among published studies, there is no definitive proof that cranberry juice is effective or useless as UTI prophylaxis.

INTRODUCTION

Urinary tract infection (UTI) is one of the most common bacterial infections. Women are particularly susceptible to UTIs, and up to 60% will develop a UTI in their lifetime[1]. Of the women who experience an initial infection, approximately 5% will suffer from multiple recurrences within a year[2]. The recurrent nature of these infections are a detriment to quality of life, and the treatment required for both active infection and prevention results in substantial cost and inconvenience. Treatment for infection and prophylaxis typically consists of antibiotic therapy. While this protocol has proven to be very effective, reliance upon it has led to increasing microbial resistance, including *Escherichia coli* resistant to trimethoprim-sulfamethoxazole and ciprofloxacin[3]. Eventually, the predominant cause of UTIs may be bacteria for which there is no effective antibiotic treatment. It is imperative that a reliable alternative to antibiotic treatment be developed for UTI prophylaxis that will allow physicians to reserve antibiotics for only the most severe cases. Such an option may be readily available in the form of the American cranberry; a well-known folk remedy for treating UTIs that has seen limited application in clinical practice[2]. It is thought that proanthocyanidin, a component of cranberry juice, prevents bacteria from adhering to the epithelium of the urinary tract and causing infection[2]. Recent studies have begun investigating the effectiveness of cranberry juice as prophylactic treatment for recurrent UTIs, may soon build towards a consensus upon which clinicians can act.

CLINICAL SCENARIO

AZ is a 29 year-old female who presents with a two-day history of dysuria, hematuria, urinary frequency and urgency. This is her fourth episode in the past six months; each prior episode has been successfully treated with nitrofurantoin. She has not had any fevers, nausea, vomiting, or suprapubic, abdominal, or flank pain. She has no other medical conditions and is not currently sexually active. Physical exam is unremarkable. She read in a magazine that drinking a glass of cranberry juice every day may prevent this from happening again and she asks whether she should start doing this.

CLINICAL QUESTION

Among adult women with a history of recurrent UTI, does a daily dose of cranberry juice, as compared to placebo, reduce the UTI recurrence rate in a six-month period?

METHODS

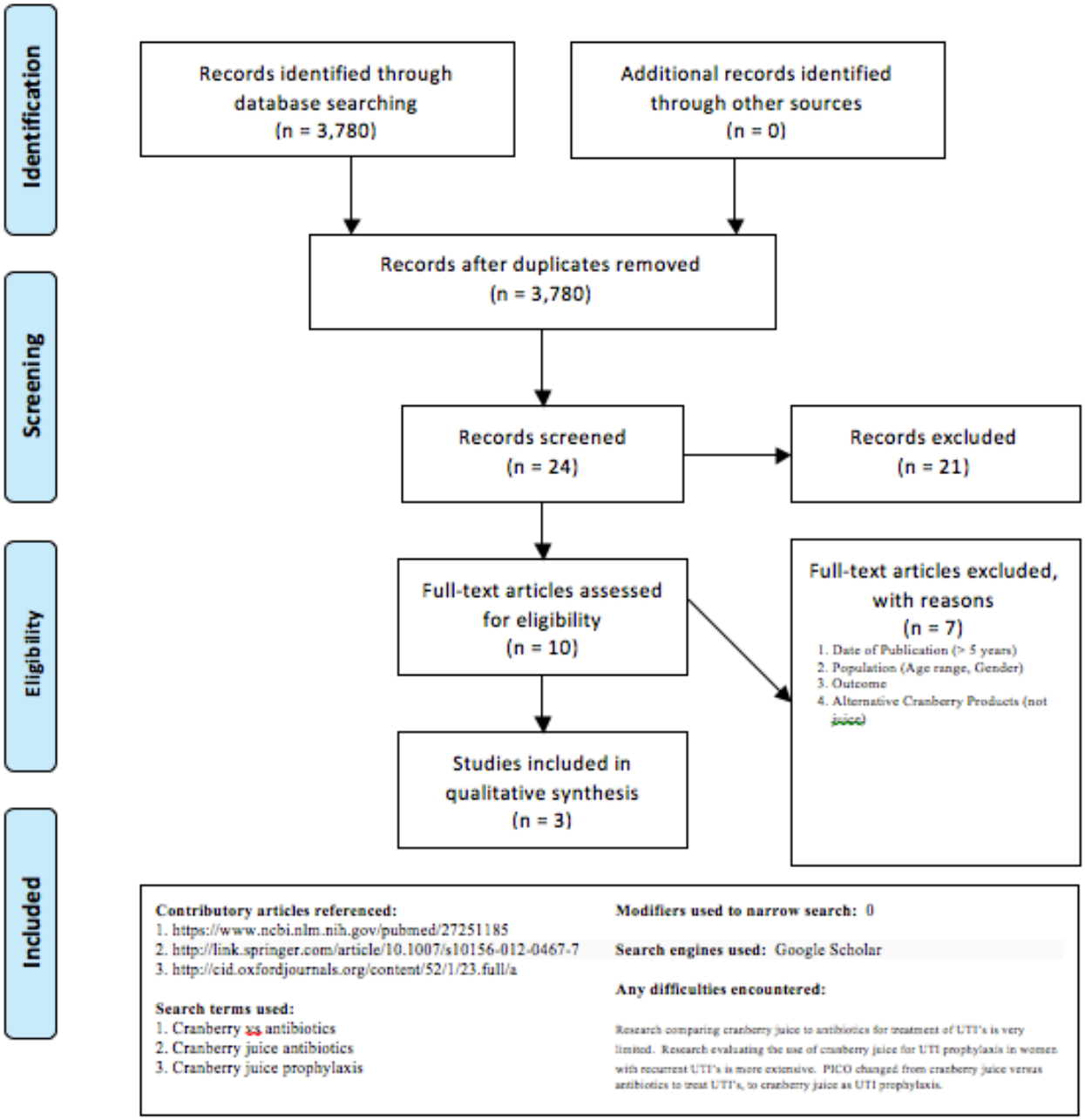
An initial search for relevant studies was conducted using Google Scholar in September 2016 (Figure 1.1). Search terms used included "cranberry vs. antibiotics", "cranberry juice antibiotics", and "cranberry juice prophylaxis". Searches for "cranberry vs. antibiotics" and "cranberry juice antibiotics" revealed that the number of available studies comparing the effectiveness of cranberry juice to antibiotics for the treatment of UTIs is very limited. The clinical

question was adjusted to reflect an investigation of the effectiveness of cranberry juice for UTI prophylaxis. The search for "cranberry juice prophylaxis" yielded 3,780 results. Of this initial yield, 24 records were screened, and ten full text articles were assessed for eligibility. Seven full text articles were subsequently excluded based on the following criteria:

- Date of Publication (> 5 years)
- Population (Age Range, Gender)
- Outcome
- Alternative Cranberry Products (Not cranberry juice)

The exclusion criteria produced a final yield of 3 studies best suited to addressing the clinical question.

Figure 1.1 PRISMA Flow Diagram



RESULTS

Study 1: *Consumption of a Cranberry Juice Beverage Lowered the Number of Clinical Urinary Tract Infection Episodes in Women With a Recent History of Urinary Tract Infection. Maki et al.*[1]

Study Objective: To compare the effects of the consumption of a cranberry beverage with that of a placebo beverage on the clinical (symptomatic) UTI incidence density in healthy women with a recent history of UTI.

Study Design: This was a 24-week, randomized, double-blind, placebo-controlled trial held from February 2013 to March 2015. Seventeen clinical research sites in the United States and one clinical research site in France were the study locations. A sample size of 145 subjects per group was calculated to provide ≥ 80% power. An enrollment of 340 subjects (170 subjects per group) was planned. See Table 1.1 for inclusion and exclusion criteria.

Table 1.1 Study 1 Inclusion & Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Women 20-70 years old • Body mass index (BMI) ≤ 40 kg/m^2 • Recent history of UTI, defined as self-report of ≥ 2 UTIs treated by a healthcare professional, of which ≥1 within 6 months of screening visit	• Prophylactic antibiotic use for UTI • Active infection or signs and symptoms of UTI or other active infection • Use of bladder catheter • History of renal or urinary tract disease, anatomic abnormality, or previous urologic surgery • Spinal cord injury, multiple sclerosis • Immunocompromising conditions • Diabetes mellitus with glycated hemoglobin ≥ 8% or treatment with insulin • History of cancer within previous two years • Major trauma or surgical event within previous three months • Anticoagulant use within previous 4 weeks • Women planning to become pregnant during the study, pregnant women, and lactating women • Women with abnormal labs of clinical importance

Subjects were assigned via a randomizing computer program to consume one eight-ounce (240 mL) bottle of cranberry beverage, provided by Ocean Spray Cranberries Incorporated, or placebo study beverage, a formulation with similar juice content and undetectable levels of proanthocyanidin and other bioactives, per day throughout the 24-week treatment period. Each bottle of cranberry juice contained a mean proanthocyanidin concentration of 119 ± 16.9 mg. Subjects kept daily diaries of their study product consumption and urinary symptoms, and returned all unused and empty bottles of study product to the clinic to assess compliance. The diaries were then checked against the number of unused and empty bottles at random intervals to ensure validity.

Clean-catch urine specimens were obtained at weeks -1, 0, 8, 16, and 24 for urinalysis and culture. A leukocyte esterase dipstick result determined the presence or absence of pyuria. If UTI symptoms occurred at any time during the study, the subject returned to the clinic for a UTI-assessment visit; these visits included a pelvic examination and clean-catch urine specimen collection. An investigator diagnosis of UTI was made based on the presence of at least one of the following urinary symptoms: dysuria, urgency, frequency, or suprapubic pain in the absence of other potential etiologies.

The primary outcome measured was the clinical UTI incidence density, defined as the number of clinical UTI events in each group (including multiple events per subject when applicable) per unit of observed time. Secondary and exploratory outcomes included the incidence density for UTI with pyuria and time from random assignment to first UTI; first UTI with pyuria; and first symptomatic UTI with positive culture ($\geq 10^3$ CFU/mL) for any uropathogen or *E. coli*.

The characteristics of the study groups were compared using analysis of variance (ANOVA), which determines whether the means of several groups are equal, and chi-square tests, which compare observed and expected data with the assumption that no differences between them exist (null hypothesis). Intent-to-treat analysis, which includes all randomly assigned subjects regardless of deviation from study protocol (i.e. due to non-compliance, loss to follow-up, withdrawal, etc.), was performed with observation time adjusted at the time that the study product was discontinued for subjects who did not participate for the full 24 weeks. Poisson regression, which assumes that variable responses occur with a known average rate and independently of each other, was used to analyze the UTI incidence density with respect to treatment, site, country (United States or France), time since last UTI category (≤30, 31-89, or ≥90 days), and age subgroup (≤50 or >50 years). Time-to-event outcome variables were analyzed using Cox proportional hazards models, which demonstrate the number of new cases of disease per population at-risk per unit time, with these same covariates, and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated.

Study Results: Three hundred seventy-three subjects were randomly assigned to either the cranberry group (n= 185) or the placebo group (n= 188), and 322 subjects completed the study [cranberry: n= 160 (86.5%); placebo: n= 162 (86.2%)]. The average age of study participants was 40.9 years, and there were no significant differences between the cranberry and placebo groups with respect to age, age subgroup, race, ethnicity, number of recent UTIs in the past 6 months, days since last UTI, vaginal intercourse frequency, number of sexual partners in the previous 4 weeks, history of diabetes, BMI, number of alcoholic drinks per week, or smoking status.

Within the cranberry group, 39 of 53 UTI-assessment visits resulted in an investigator-diagnosed UTI. Within the placebo group, 67 of 82 of these assessments resulted in an investigator-diagnosed UTI. There was a significant reduction in the UTI incidence density between the cranberry and placebo groups (incidence rate ratio: 0.62, 95% CI: 0.42-0.92; p= 0.017), as well as the incidence density for symptomatic UTIs with pyuria (incidence rate ratio: 0.63, 95% CI: 0.40-0.97; p= 0.041). These results are shown in Tables 1.2 and 1.3. Thirty-three of the subjects in the cranberry group compared to 50 subjects in the placebo group experienced a first symptomatic UTI at the end of 24 weeks (HR: 0.67, 95% CI: 0.43-1.05, p= 0.078). There was no significant difference in the treatment response for subjects ≤50 and >50 years old. There were no significant differences between the study groups with respect to time from random assignment to first clinical UTI with pyuria (HR: 0.69, 95% CI: 0.43-1.12, p= 0.131), positive culture (HR: 0.97, 95% CI: 0.56-1.67, p= 0.914), or positive E. coli (HR: 1.38, 95% CI: 0.73-2.59, p= 0.323).

Table 1.2 Subjects Reporting Symptomatic Episodes of Investigator-Diagnosed UTI

Episodes, *n*	Cranberry group (n= 185)	Placebo group (n= 188)	Incidence rate ratio (95% CI)	*p*
0	152 (82.2%)	138 (73.4%)	--	--
1	27 (14.6%)	36 (19.2%)	--	--
2	6 (3.2%)	11 (5.9%)	--	--
3	0 (0.0%)	3 (1.6%)	--	--
≥ 1	33 (17.8%)	50 (26.6%)	--	--
Total UTIs, *n*	39	67	--	--
Annualized incidence density (95% CI)	0.48 (0.33-0.63)	0.75 (0.56-0.94)	0.62 (0.42-0.92)	0.017

Table 1.3 Subjects Reporting Symptomatic Episodes of UTI with Pyuria

Episodes, *n*	Cranberry group (n= 185)	Placebo group (n= 188)	Incidence rate ratio (95% CI)	*p*
0	157 (84.7%)	147 (78.2%)	--	--
1	24 (13%)	31 (16.5%)	--	--
2	4 (2.2%)	8 (4.3%)	--	--
3	0 (0.0%)	2 (1.1%)	--	--
≥ 1	28 (15.1%)	41 (21.8%)	--	--
Total UTIs, n	32	53	--	--
Annualized incidence density (95% CI)	0.40 (0.39-0.41)	0.59 (0.58-0.61)	0.63 (0.41-0.98)	0.041

Study Critique: The blinding of both the investigators and the subjects is a major strength of this study, as it minimizes investigator bias and the placebo effect. Subjects were unable to reliably guess which beverage they were assigned to receive, further reducing the placebo effect. Because there was no significant heterogeneity between the study groups, obvious confounding variables were kept to a minimum. The study claims to be the largest to date to assess the effect of cranberry juice consumption on UTI occurrence, but 67 percent (250/373) of the subjects were white, which may not represent the full spectrum of female patients seen for UTI. Furthermore, there may have been recall bias with self-reports of ≥2 clinician-treated UTIs in the past year, one of the inclusion criteria, which may have skewed the study population to include more women who do not experience recurrent UTIs, thereby increasing the probability of a Type II error. The study boasts 98% compliance and 86% completion, another major strength. While self-reports may have overestimated the true compliance rate, the researchers effectively anticipated this possibility and included appropriate "safety nets" (random checks of daily consumption diaries and requiring subjects to return all product bottles, empty or unused) accordingly.

Study 2: *A Randomized Clinical Trial to Evaluate the Preventive Effect of Cranberry Juice (UR65) for Patients with Recurrent Urinary Tract Infection. S Takahashi et al.*[4]

Study Objective: To evaluate the effectiveness of cranberry juice as UTI prophylaxis for patients with a history of recurrent UTI.

Study Design: The study was a randomized, placebo-controlled, double-blind clinical trial. The subjects included in the study were patients from 20 to 79 years of age presenting to urology clinics in Japan with acute uncomplicated cystitis or chronic complicated cystitis. All of the subjects

had a history of multiple UTI relapses that had been successfully treated with antibiotics. Subjects who met the initial criteria for study participation were subsequently excluded for reasons summarized in Table 2.1.

Table 2.1: Study 2 Inclusion & Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• 20 to 79 years of age • Presenting to urology clinics in Japan with acute uncomplicated cystitis or chronic complicated cystitis • History of multiple UTI relapses that had been successfully treated with antibiotics	• History of uric acid stone disease • Required urological manipulation for urinary tract stone disease, urinary tract obstruction, or urinary tract malignant disease • Use of an indwelling urinary catheter • Concomitant urogenital infection • Systemic diseases or severe complications • History of allergic reaction to cranberry products • Judged to be ineligible by a doctor

After the exclusion criteria were applied, the subjects were randomly assigned to a cranberry juice group (Group A) or a placebo beverage group (Group P). The color and taste of the cranberry juice and placebo beverage were modified to ensure the subjects were unaware of which treatment they were receiving. The cranberry juice was a formulation designated UR65 and contained at least 40 mg of proanthocyanidin per 125 mL. Depending on their group assignment, subjects drank one bottle (125 mL) of UR65 or the placebo beverage once daily, before sleeping, for 24 weeks. Follow up visits were conducted every four weeks at the urology clinics, where each subject was interviewed regarding any symptoms, adverse events, the frequency of UTI relapses in the past year, and compliance with daily consumption of the assigned beverage. The endpoint of the study for each participant was the diagnosis of a UTI relapse followed by treatment with antibiotics.

For statistical analysis, the Kaplan-Meier method was applied to calculate the cumulative relapse free rate at the time that each UTI relapse was diagnosed. The log-rank test was utilized to determine the statistical significance of any differences observed in the Kaplan-Meier curves (alpha = .05, power = 0.2). Cox's proportional hazards model was used to conduct multivariate analysis and determine the factors for UTI relapse.

Study Results: Two hundred thirty-seven subjects were initially screened and 213 were ultimately registered for the study (Group A n= 107, Group P n= 106). The median age of Group A subjects was 55 years and subjects in Group P had a median age of 59 years. There was no significant difference between groups with respect to demographics and only one participant was lost due to an adverse event.

There was no significant difference in the UTI relapse rates of Group A and Group P (log-rank test, p = 0.4209) (Figure 2.1). When a subset of 170 participants with acute uncomplicated cystitis were analyzed separately, there was no significant difference in the UTI relapse rates of Group A and Group P (log-rank test, p = 0.1300). Of these 170 subjects with acute uncomplicated cystitis, 52 were less than 50 years of age and 118 were older than 50 years of age. For subjects ≤50 years of age with acute uncomplicated cystitis, there was no significant difference in the UTI relapse rates of Group A and Group P (log-rank test, p = 0.3623). However, for subjects >50 years of age, a significant difference in the UTI relapse rates of Group A and Group P was observed (log-rank test, p = 0.0425) (Figure 2.2); 16 of 55 subjects (29.1%) in Group A experienced a UTI relapse, and 31 of 63 subjects (49.2%) in Group P experienced a UTI relapse.

Multivariate analysis was applied to the study of subjects older than 50 years of age to determine the causes of the UTI relapse, and revealed that drinking cranberry juice had a marginally significant prophylactic effect against relapse, and aging was a significant factor. Conversely, a history of UTI relapses in the past year was not associated with relapse.

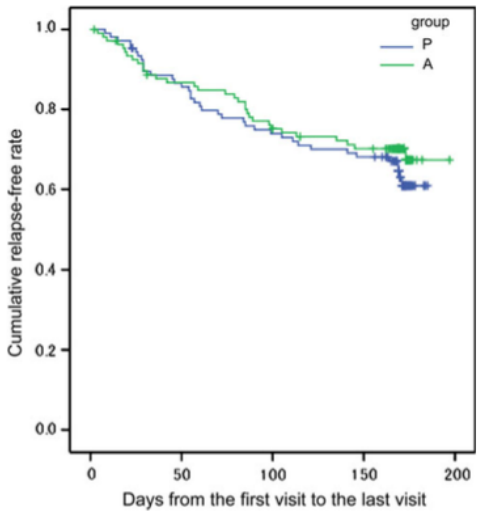


Figure 2.1: Cumulative non-relapse rates in Cranberry Juice Group (A) and Placebo Group (P) (Log-Rank Test, p = 0.4209)

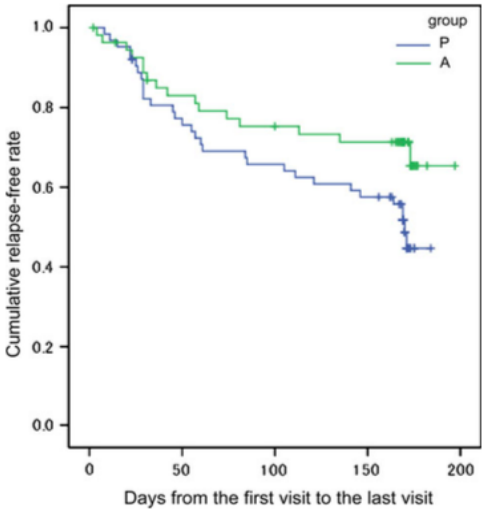


Figure 2.2: Cumulative non-relapse rates in Cranberry Juice Group (A) and Placebo Group (P) in the subjects ≥ 50 with acute uncomplicated cystitis (Log-Rank Test, p = 0.0425)

Study Critique: As a randomized, double-blind, placebo controlled study, the researchers made considerable effort to minimize the intrusion of bias and confounding variables, but it was not clear from the description of their methodology that they succeeded. Additional insight into their procedures might demonstrate that their study design was as strong as intended, or they might need to revise their approach in future attempts. With regards to double-blinding, it is clearly stated that the subjects were randomly assigned to one of two groups, but what steps were taken to ensure that the researchers were not aware which subjects were in which group? It is stated that the cranberry juice and placebo beverage were modified to make them indistinguishable, but were they tested to make sure subjects would not be able to tell the difference between them?

In several aspects of the study design, important issues were addressed but were either vaguely or inadequately explained, and need clarification. UR65 is identified as the cranberry juice that was tested but the researchers do not explain the origin of UR65. Is it their designation for a

commercial brand or is it their unique formula that they may propose recommending to patients? When were the subjects supposed to take their daily dose of UR65? The study indicates that they were to take their dose before they went to sleep, but was it clear to the subjects that this would be at night, or could they have been led to believe they could take the dose anytime before going to sleep, such as before an afternoon nap?

Subject inclusion and exclusion would have benefitted from more clearly defining what subjects were of interest. Were study participants experiencing an active UTI at the start of the study? The methodology is worded as if they sought patients presenting to clinics with acute uncomplicated cystitis or chronic complicated cystitis, but it would not make sense to evaluate UTI relapse if subjects started the study with an active UTI. If these subjects presented with a UTI and were then treated with antibiotics before beginning the study, this should have been specified, in addition to making it clear how soon their participation began following treatment. The exclusion criteria was clearly stated and helped to narrow down the researchers' population of interest, but the final entry in the criteria was vague, giving screening physicians the authority to designate a potential subject ineligible according to their judgment. Guidelines for exclusion should be given for the physicians to follow rather than having them resort to open-ended judgment that could introduce bias.

This study also would have benefitted from a more rigorous approach to compliance and defining subject background. It is stated that doctors "strictly confirmed" compliance during periodic interviews, but it is not explained how this was accomplished. Interviewing alone would result in a great deal of uncertainty regarding compliance; more tangible measures such as having the subjects turn in their beverage bottles would have been more effective. With respect to subject background, the researchers explain that there is no significant difference in the backgrounds of their subjects that would influence the rate of UTI relapse, but the table in the study that summarizes subject background gives no indication of patient lifestyle, occupation, or socioeconomic status. The only background information provided is age, recent history of UTI recurrence, previous antimicrobial treatment, and the fact that the participants are all Japanese. This limited selection of population characteristics makes it difficult to apply the study's findings to other clinical settings. Had the researchers included specific background information that provided more insight into the subjects' risk factors for UTI, it may have been more feasible to extrapolate the data to subjects beyond the Japanese sample population.

This study might also benefit from being repeated with a narrower age range that represents a specific level of risk for UTI. The researchers narrowed down the age range as the study progressed but were left with a limited sample size. Focusing on a more specific age group from the beginning of the study will increase their sample size and lead to results more useful for that demographic.

Study 3: *Cranberry Juice Fails to Prevent Recurrent Urinary Tract Infection: Results From a Randomized Placebo-Controlled Trial. Barbosa-Cesnik et al.*[2]

Study Objective: To determine the effect of regular consumption of cranberry juice on the rate of urinary tract infection (UTI) recurrence, and on the duration of UTI symptoms

Study Design: The study was a prospective, randomized, double-blind comparison of the effectiveness of cranberry juice with that of a placebo in preventing the recurrence of UTI. Study participants were recruited from women presenting to the University of Michigan Health Service laboratory for a urinalysis due to UTI symptoms. A sample size of 120 subjects per group was calculated to provide ≥ 80% power. An enrollment of 400 subjects (200 subjects per group) was planned.

Women interested in participating were enrolled if they were 18-40 years of age, had at least three UTI symptoms and would be in the vicinity of the laboratory for the next six months. Recruitment of participants took place during the fall semester of each year of the study to increase the likelihood that potential participants would be available for the designated study period. Interested participants were subsequently excluded for reasons summarized in Table 3.1:

Table 3.1: Study 3 Inclusion & Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Women presenting to the University of Michigan Health Service laboratory for a urinalysis due to UTI symptoms • 18-40 years of age • ≥3 UTI symptoms • In the vicinity of the laboratory for the next 6 months	• Received antibiotic treatment within 48 hours prior to enrollment • Hospitalization or catheterization within the previous two weeks • Kidney stones • Diabetes • Pregnancy • Cranberry allergy • Negative urine culture result

The cranberry juice was a research grade low-calorie juice cocktail (LCJC) provided by Ocean Spray Cranberries created using *Vaccinium macrocarpon Aiton* cranberries. The treatment protocol for the study required that participants drink one eight-ounce (240 mL) bottle of their assigned beverage twice per day for the duration of their involvement in the study. The batches of LCJC were adjusted to maintain consistent proanthocyanidin concentration. Each eight-ounce dose of LCJC contained a mean proanthocyanidin concentration of 112 ± 14.1 mg. Ocean Spray also provided the placebo juice, which was designed to imitate the flavor and color of their cranberry juice. The LCJC and placebo juice were packaged in identical bottles and stored in refrigeration until distributed to participants. To maintain a consistent level of cranberry consumption among any participants assigned LCJC, all participants were instructed to refrain from eating any cranberry or blueberry products during their participation. In an effort to maintain a high level of compliance, the beverages used in the study were conveniently delivered to the participants' homes every one to two weeks.

Upon enrollment, participants were randomly assigned a treatment beverage of either cranberry juice or a placebo juice, performed by the Data Coordinating Center (DCC) at the University of Michigan. Concealment of who was allocated which juice was maintained by entering the participants' lot numbers into a web-based enrollment form at the start of the study. This resulted in a database that could be used when it was time to provide more juice. Researchers simply entered lot numbers into the same web-based form, which then replied with which juice to provide. The DCC knew which lot numbers were assigned to which participants, but this information was withheld from the researchers to keep them blinded.

Each participant began the study with a clinical visit where they were screened for uropathogens by providing clean-catch urine specimens and self-collected vaginal and rectal specimens. All urine specimens were cultured, and a positive culture was defined as ≥1000 CFU/mL urine of a known uropathogen. Additional specimens were collected at clinical visits three months and six months into the study and at any additional visits prompted by the development of UTI symptoms. Participants also completed questionnaires at each clinical visit that assessed UTI symptoms, risk and behavioral factors associated with their UTIs, diet, compliance, gastrointestinal symptoms, and medical history. Additional interviews were conducted via phone or email three days, one week, two weeks, one month, two months, four months, and five months after enrollment.

Compliance with the protocol of this study depended on self-reporting through participant response to the questionnaire provided at clinical visits. Subjects were instructed to contact the

researchers if they experienced any UTI symptoms. In the event that symptoms developed when the clinic was inaccessible, all participants were given a sample collection bag. Participants who developed UTIs were treated with antibiotics by their regular physicians. The medical records of all participants were reviewed after the study to document any UTIs that might not have been reported.

The endpoint for the study participants was six months of participation or the diagnosis of a UTI, whichever occurred first. For a UTI to end study participation, it had to develop ≥15 days after enrollment. If a UTI developed within 15 days of enrollment, it represented the end of participation only if a subsequent culture revealed a different uropathogen than that which prompted initial enrollment. Intent-to-treat analysis was performed for subjects who did not complete the entire study.

Study Results: Three hundred nineteen women were eligible for the study and were randomly assigned to either the LCJC group (n=155) or the placebo group (n=164). Of the 319 women originally enrolled and assigned to one of the two study groups, 230 completed the entire protocol, including 116 who received the LCJC treatment and 114 who received the placebo juice. The average age in each group was 21 years and almost all participants had a history of at least one UTI. There were no significant differences in the demographics, behavioral characteristics, or medical histories of the treatment and placebo groups. Ninety-eight percent of participants were sexually active, including vaginal intercourse an average of two to three times per week. Most of the participants were college students and less than ten percent in each group were married. The most common organism isolated on the initial urine cultures collected from each group was *E. coli*. The self-reported compliance was similar between the two groups.

Fifty-four recurrent UTIs were verified with urine cultures, an overall recurrence rate of 16.9 percent. Thirty-one of these recurrent UTIs developed in participants given LCJC (19.3%) and 23 developed in those given placebo juice (14.6%), which was not a statistically significant difference (log-rank test, p = 0.21) (Figure 3.1). The development of urinary and vaginal symptoms was similar for both groups at three days, 1-2 weeks, and greater than one month into the study.

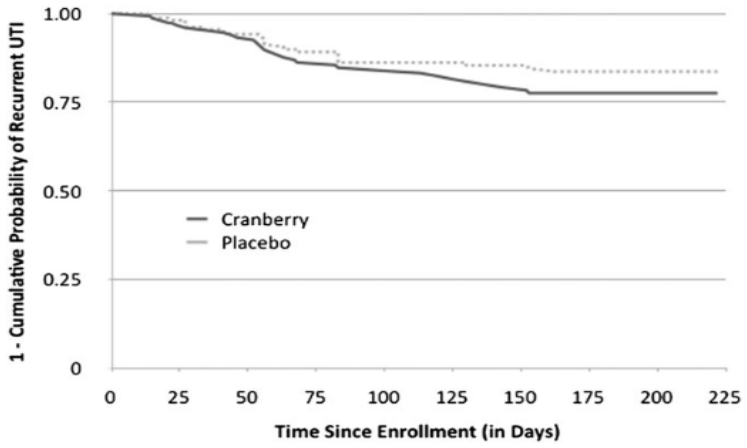


Figure 3.1: Time to UTI recurrence for groups receiving Cranberry Juice versus Placebo Juice (log-rank test, p = .21)

The results of the study were further analyzed to adjust for sexual activity and history of UTIs, two known predictors of UTI recurrence. Adjusting for these factors made no difference in the risk of recurrence with each treatment. In those participants who did not develop a UTI, there was no difference in the frequency of sexual activity during the month before the study began, and the last month of study. The risk of a recurrent UTI was significantly higher in those with a history of two or more UTIs, but the LCJC did not have any significant effect on the risk of UTI in recurrence in those with or without a history of UTIs.

Study Critique: The strength of this study was evident upfront with the choice of cranberry treatment, and the care that was taken to learn useful information from it. The researchers collaborated with Ocean Spray, who produces popular retail cranberry juice. By working with Ocean Spray, the study would ultimately generate useful information about the effectiveness of a product the general population uses and to which it has easy access. Testing the treatment juice against the placebo to ensure they were indistinguishable would have been a worthwhile step, however, and is worth considering in future studies.

The researchers were very detailed in the design and implementation of the study protocol. They targeted a very specific demographic, college-age women, and were able to quickly select a sample of participants by recruiting from women visiting a university health clinic for purposes of UTI urinalysis testing. Urine cultures confirmed history of at least one UTI; this was an essential step for study with the stated goal of testing the effectiveness of cranberry juice in preventing *recurrence*. Furthermore, the researchers were meticulous in their random assignment of participants and preservation of the double-blind nature of the study. Another strength was the care taken to provide participants with clear instructions with regular follow-up i.e. how much juice to drink and how often, when contact the clinic, self-collect urine specimens in the event the clinic is unavailable. Because participants were specifically instructed to avoid any cranberry or blueberry products other than the juices provided by the researchers for the duration of the study, interference in evaluating the effectiveness of cranberry juice was probably kept to a minimum

Protocol compliance was essential to the study's success and was a point of emphasis with all participants. Increased compliance was aided by the decision to have all juice delivered to the participants' homes, and by having compliance self-reported on frequently administered questionnaires. These measure to encourage compliance were a good start, but compliance would have been more effectively monitored participants had been required to return the empty bottles.

The additional effort made to account for differences in the two study groups that might have influenced the results is yet another strength of this study. They compared the demographics, behavior, and medical history of the two groups, and found them to be similar. They also accounted for any differences in sexual behavior and UTI history, two factors known to increase the risk of developing a UTI, thereby limiting confounding variables. The UTI risk of each group was assessed using an intent to treat analysis, which improves the study's applicability to clinical practice by including any participants lost to follow up and taking into account inevitable non-compliance.

The results of this well-designed study provide a useful indicator of the effectiveness of cranberry juice for UTI prophylaxis for college-age women, but has limited usefulness outside of this narrowly defined group. Future studies might consider recruiting participants at clinics that serve a more diverse patient base in an effort to improve the generalizability of the results.

DISCUSSION

Current studies regarding the effectiveness of cranberry juice consumption in preventing recurrent UTIs provide conflicting results. The findings from this review are no exception given the apparent heterogeneity between the selected studies with respect to the average age of participants, amount and type of cranberry juice or placebo ingested daily, diagnostic criteria for recurrent UTI, and primary outcome measured. Table 4.1 summarizes the findings of the reviewed studies.

Table 4.1 Overall Comparison of Reviewed Studies

Authors	Study 1: Maki et al.	Study 2: Takahashi et al.	Study 3: Barbosa-Cesnik et al.
Design	Double-blinded RCT	Double-blinded RCT	Double-blinded RCT
Population size (n) **(Study, Placebo)**	n= 373 (185, 188)	n= 213 (107, 106)	n= 319 (155, 164)
Age range participants **Average age** ***Median age**	21-70 years 40.9 years	20-79 years 55 years* (study group) 59 years* (placebo)	18-40 years 21 years
Amount cranberry juice **[Proanthocyanidin]**	240 mL once a day for 24 weeks 119 ±16.9 mg/240 mL	125 mL once a day for 24 weeks >40 mg/125 mL	240 mL twice a day for six months 112 ± 14.1 mg/240 mL
Diagnostic criteria for recurrent UTI	Presence of dysuria, urinary urgency, frequency, and/or suprapubic pain	Not specified	Presence of UTI symptoms and positive uropathogen culture from urine, vaginal, or rectal specimen
Primary outcome	Clinical UTI incidence density (number UTI events/time)	UTI relapse rate	UTI relapse rate
Results	Significant reduction in UTI incidence density (p=0.017)	No significant difference in overall UTI relapse rates (p=0.42) Significant difference in subjects >50 y (p=0.042) **(Figure 2)**	No significant difference in UTI relapse rates (p=0.21) **(Figure 3)**

Studies from Maki et al. and Barbosa-Cesnik et al. seem to have the most similar methodologies, yet arrive at opposing conclusions. Both offered Ocean Spray cranberry products for about 24 weeks and included urinary symptoms and positive urine culture in the diagnostic criteria for recurrent UTI, but Barbosa-Cesnik et al. demonstrated no significant difference in UTI relapse rates between groups despite study participants drinking twice the amount of cranberry juice compared to those in the Maki et al. study; in fact, the cranberry group presented a higher UTI recurrence rate than the placebo group (20% vs. 14%). While Takahashi et al showed a significant difference, albeit slight, in the UTI relapse rates in subjects over 50, Maki et al reported no such significant UTI reduction among participants over or under 50, despite both groups having a similar number of participants over 50 (118 and 109, respectively). Still, this small sample size makes it difficult to generalize to a larger population, especially since the outcomes differ. Takahashi et al. and Barbosa-Cesnik et al. both looked at the UTI relapse rate as the primary outcome but did not calculate the relapse rate ratio, which could have been easily accomplished (rate of recurrent UTI in cranberry group/rate of recurrent UTI in placebo group). Maki et al. looked

at the UTI incidence density, which inherently implies that a UTI relapse has occurred (i.e. can be seen as a sort of relapse rate ratio), as the primary outcome. Thus, the incidence rate ratio may have been comparable to the relapse rate ratios found in the other two studies had they chosen to calculate them.

Maki et al. had the largest sample size and clearly had the most rigorous inclusion/exclusion criteria, compliance verification, and statistical analysis, which therefore deems it the most applicable to the general population of the three studies evaluated in this review; however repeated studies with the same methodology may be needed in order to ensure the validity of the original findings.

The use of cranberry pills for UTI prophylaxis has also been studied, and superficial review revealed that it might be more effective than that of cranberry juice[5,6]. Fortunately, proanthocyanidins have not been associated with any consistent side effects, and no herb-drug interactions have been reported[7,8]. Because of this, there is no harm in supporting patients' decisions to add cranberry products to their daily regimen if they believe it will help prevent future UTIs.

CONCLUSION

UTIs affect all patient populations, and there are many different risk factors and subgroups that increase the likelihood of morbidity. As a result, there is significant heterogeneity among published studies that evaluate the use of cranberry juice as prophylaxis for recurrent UTI. This makes it nearly impossible to draw a generalized conclusion regarding its use for all patients; instead, its worth and subsequent use as preventive treatment should be guided by studies with populations that closely resemble the patient. For women with a history of recurrent UTI, more information is needed in order to definitively recommend or refute cranberry juice as prophylactic therapy.

For our patient AZ, we would discuss with her that there is no definitive answer regarding the effectiveness of cranberry juice in preventing UTIs, given the vast differences between the methodologies and conclusions of the studies available today. Cranberry juice is, however, safe overall, and we encourage her to use it if she feels that it will make a difference and does not cause any inadvertent health problems for her specifically.

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