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Cranberries for women with recurrent urinary tract infection: a meta-analysis

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ABSTRACT

BACKGROUND Cranberries are the most widely used nonantibiotic prophylaxis for recurrent urinary tract infection (rUTI) in women; however, their efficacy still remains uncertain. Hence, this meta-analysis was aimed to assess the effectiveness, safety, and adherence of cranberry as a prophylactic drug for treating rUTI.

METHODS Literature search was conducted using PubMed, EBSCO, Science Direct, Scopus, Cochrane, and Google Scholar. Studies were screened for duplication, inclusion and exclusion criteria, and then reviewed by two authors independently. This included all randomized controlled trials of cranberry derivatives *versus* placebo and antibiotic prophylaxis. Cochrane risk-of-bias assessment tools were used to evaluate the quality of the study. Quantitative analysis was performed using the Review Manager 5.0 software.

RESULTS Nine studies were included. Among 1,542 participants, cranberry consumption reduced incidence of rUTI in women compared with placebo (p = 0.02). The subgroup analysis revealed that only cranberry capsules were superior to placebo (relative risk [RR] = 0.67, 95% confidence interval [CI] = 0.45–0.98), but not for cranberry juice (RR = 0.85, 95% CI: 0.7–1.04). Antibiotics had better outcome than cranberry for rUTI (RR = 0.83, 95% CI = 0.70–0.98). Most of the participants experienced minor adverse events such as rash and gastrointestinal symptoms. There was also a good adherence rate, ranging from 90.3–99% monthly dose.

CONCLUSIONS Cranberry, especially cranberry capsule consumption, had a significant effect in reducing the incidence of rUTI compared with placebo, with good adherence rates, and minor adverse events. In contrast, although antibiotic use had a greater efficacy, it was associated with a higher risk of severe adverse events.

KEYWORDS cranberry, prophylaxis, urinary tract infection, women

Urinary tract infection (UTI) is a condition where numerous bacteria are present in a certain amount (generally 10^5 colony forming unit per milliliter [CFU/ml]) and results in various types of diseases such as cystitis and pyelonephritis.[1] This disease is the most frequent bacterial infection and has been reported to account for a significant burden across the world, with 150 million people being affected each year.[2] Based on registries in the United States, the prevalence of community-associated UTI has been found to be 0.7%, with women comprising the predominant group.[3] In Indonesia, Sugianli et al[4] reported that among 3,424 eligible patients in public and private hospitals and clinics, 840 had positive cultures. Several pathogens are suspected to cause UTI, among which *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus faecalis*, and *Staphylococcus saprophyticus* are the most

common.[2] After an infection with these pathogens, especially *E. coli*, *S. saprophyticus*, *K. pneumoniae*, and *P. mirabilis*, UTI may lead to recurrent UTI (rUTI) in 25–35% of healthy females.[5, 6]

Recurrent UTI is defined as a UTI (proven by culture) with episodes of uncomplicated UTI for more than three times a year or more than two episodes in 6 months. The incidence of rUTI was found to be high in the primary care setting, ranging from 36% in younger women to 53% in women aged >55 years.[6] Data regarding the burden of UTI and rUTI are conflicting according to each study. Some studies report that rUTIs are not life-threatening, although a reduced quality of life and increased healthcare costs are inevitable in these diseases.[7] Patients with rUTI may experience the anxiety of sudden acute episodes and psychological burden.[8] A study conducted by Mitchell et al[9] reported that 1.73% of admitted patients who had UTI had 3.5 days additional length of stay, and 2.3 times more risk of dying during their admission. Moreover, in the United States, the annual financial burden of UTI has been reported to be >$3.5 billion, whereas in Italy, the cost of treating UTI and rUTI was approximately €240, and €140 per episode, respectively.[5,10] Thus, preventive measures should be implemented to solve this problem.[5]

One of the most common methods to prevent rUTI is using antibiotics. However, repetitive use of antibiotics may lead to various side effects such as disturbances in the normal microbiota equilibrium in the body, development of multidrug resistance, and increased costs. Therefore, nonantibiotic approaches could be highly important to prevent rUTIs.[5]

Cranberries, with a history of more than 200 years of usage as a urinary antiseptic, have been one of the most widely used nonantibiotic approaches used for the prevention of rUTI. When used as a UTI prophylactic, cranberry compounds such as A-type proanthocyanidins, and other polyphenols may inhibit the binding of bacteria, including P fimbriae of uropathogenic *E. coli* that is responsible for causing almost 85% of uncomplicated UTI cases. Cranberry may also inhibit the formation of P-fimbriated *E. coli* biofilm.[5,11] Furthermore, it has recently been demonstrated that quinic acid present in cranberry induces the excretion of hippuric acid, which acts as an antibacterial agent. Other beneficial effects of cranberry include the suppression of inflammatory cascades and the attenuation of the development of uropathogenic reservoirs in the gastrointestinal tract and urothelium.[5] Various animal trials have also supported the use of cranberry in treating UTI.[11]

On the other hand, trials on human subjects have reported conflicting results regarding UTI prevention. Although the majority of trials have indicated a significant reduction of rUTI in patients who consumed cranberry, there are also trials that reported no significant effect of cranberry as a prophylaxis.[11,12] Jepson et al[12] reviewed these inconsistent results multiple times every 4 years (the last time was in 2012). Although their previous study showed that cranberry juice had a role in UTI prevention, their latest study (in 2012) reported otherwise, after adding further novel studies. This may suggest that newer studies provide different results in the current meta-analysis. Therefore, to clarify all these issues, this meta-analysis was conducted to assess the effectiveness of cranberry as a prophylaxis for rUTI in women based on current available studies.

METHODS

A literature search was conducted using several search engines, including PubMed, EBSCO, Science Direct, Scopus, Cochrane, and Google Scholar as seen in Figure 1. The keywords used were (cranberry OR cranberries OR Vaccinium) AND ("recurrent UTI" OR rUTI OR cystitis). All keywords were searched for their respective MeSH thesaurus. This searching was not limited by date of publication, and only English language articles were included. Citation alert in Google Scholar was also applied in this search process.

Criteria for studies

Types of studies

This meta-analysis used all randomized controlled trials (RCTs) of cranberry derivatives *versus* placebo and antibiotic prophylaxis. Only full-text studies were included. Unpublished articles and abstracts were excluded from the review.

Types of participants

The participants were women aged ≥18 years with a history of UTI. Children, pregnant women, those with a history of gynecological surgery, women undergoing chemotherapy, and those with an indwelling urinary catheter were excluded.

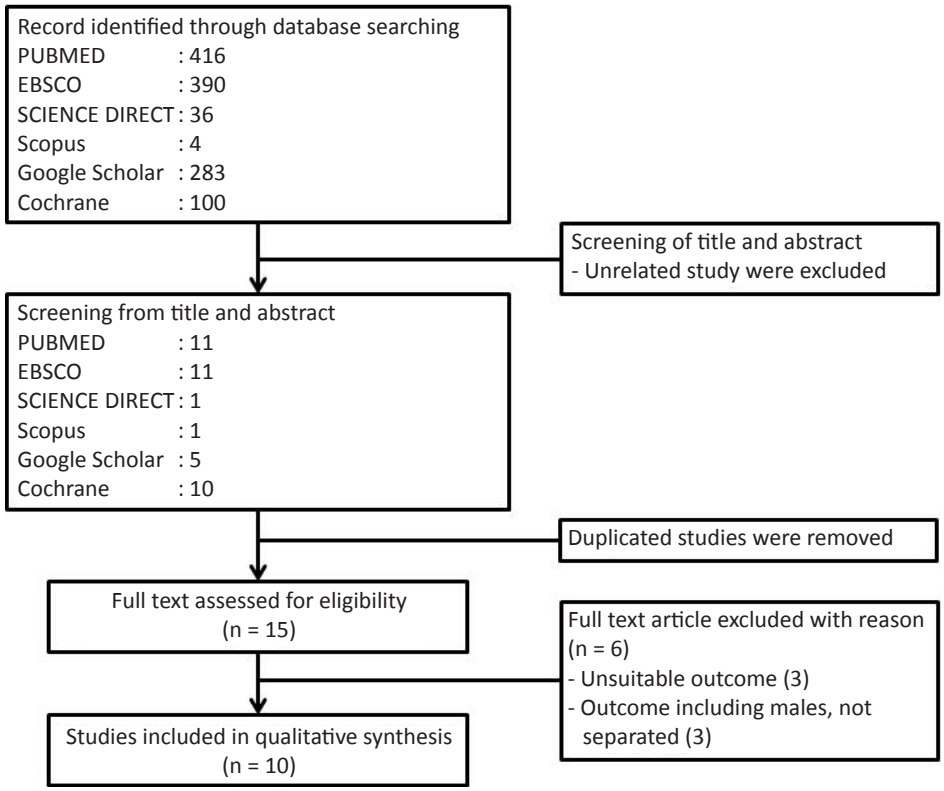

Figure 1. Study flow diagram

Types of interventions

The interventions were consumption of cranberry products compared with placebo and antibiotic prophylaxis. The various forms of cranberry included juice, capsules, tablets, powder, etc. The quantity taken per day, the concentration of the cranberry product, and the duration of treatment were also considered.

Types of outcome measures

The primary outcome of intervention was the incidence of rUTI in each group. In this study, rUTI indicated ≥2 infections occurring within 6 months or ≥3 infections in 1 year. Diagnoses were made based on signs and symptoms and confirmed by analysis of midstream specimen of urine if feasible, or a "clean catch" sample (≥10^4 CFU/ml of *E. coli* detected in the subject's urine samples). Secondary outcomes such as adverse events and adherence to therapy were also evaluated. Adverse events included minor and severe events. Adherence was determined based on the quantity of capsules ingested divided by the quantity of capsules that should have been ingested within each subject's duration of study.

Study selection and data collection

All studies were assessed manually for duplication. The titles and abstracts of duplication-free articles were selected based on inclusion and exclusion criteria, which have already been mentioned earlier. Selection of studies was done by two authors independently. Disagreement between the two authors was resolved by discussion. Thereafter, studies that met the requirements underwent full-text review. The incidence of rUTI from every eligible full-text article was extracted and analyzed.

Evaluation of biases and statistical methods

Cochrane risk-of-bias assessment tools were used in this study to evaluate the quality of the interventional study. These evaluations were conducted by two authors independently. Quantitative synthesis of selected studies was conducted using the Review Manager 5.0 software. Risk ratio was used to measure the size effects. Meanwhile, chi-square and I^2 analyzes were used to evaluate the heterogeneity of studies. A fixed-effects model was performed when $p > 0.05$, whereas a random-effects model was used when $p < 0.05$.

RESULTS

Based on the literature searching, a total of 10 studies were found to meet the selection criteria (Table 1). One study reported by Bosmans et al[13] had

to be excluded from the quantitative analysis as it had the same trial registration as that of another study reported by Beerepoot et al.[14] Therefore, the remaining nine studies were analyzed. These studies were categorized into three groups as follows: the first group compared cranberry capsules with placebo (two studies), the second group compared cranberry juice with placebo juice (five studies), and the third group compared cranberry capsules with the antibiotic trimethoprim (TMP)–sulfamethoxazole (SMX) (two studies).

Cranberry *versus* placebo for rUTI treatment

Seven trials with a total of 1,542 participants were grouped into either cranberry (capsule or juice) or placebo (Figure 2). These trials had a moderate degree of heterogeneity (p = 0.12, I^2 = 41%). In terms of rUTI, only one study conducted by Barbosa-Cesnik et al[15] reported a different result with an increased risk in cranberry consumers (RR = 1.43; 95% CI = 0.87–2.33). On the other hand, only two studies (Maki et al[16] and Vostalova et al[17]) reported a significant difference (CI of the RR <1) between the two groups. Combined analysis of these studies revealed a significantly lower incidence of rUTI in women consuming cranberry than that in women receiving placebo, with an RR of 0.81 (95% CI = 0.67–0.96).

A subgroup analysis was conducted after separating these studies into two groups based on the cranberry form, i.e., juice and capsules. There

Table 1. Characteristics of included studies

Author, year	Type of study	Subject condition	Intervention	n	Control	n	Duration
Takashi et al,[21] 2015	RCT	Women aged 20–79 years with a history of rUTI	Cranberry juice 125 ml/day (PAC = 40 mg)	107	Placebo juice 125 ml/day	106	6 months
Vostalova et al,[17] 2015	RCT	Women aged 18–75 years with a history of rUTI	Cranberry capsules 500 mg (PAC = 2.8 mg)	83	Placebo capsules	93	6 months
Maki et al,[16] 2016	RCT	Women aged 20–70 years with a history of rUTI	Cranberry juice 240 ml/day (PAC = 41.1 mg)	185	Placebo beverages 240 ml/day	188	6 months
Beerepoot et al,[14] 2013	RCT	Premenopausal women aged ≥18 years	Cranberry capsules 2 × 500 mg (PAC = 9.1 mg) + 1 placebo tablet at night	104	Placebo capsules 2 × 1 + 1 TMP–SMX tablet 480 mg at night	95	12 months
Barbosa-Cesnik et al,[15] 2011	RCT	Women aged 18–40 years presenting for urinalysis	Cranberry juice 2 × 240 ml/day (PAC = 112 mg)	155	Placebo juice 2 × 240 ml/day	164	6 months
McMurdo et al,[19] 2009	RCT	Community-dwelling women aged ≥45 years	Cranberry capsules 1 × 500 mg	69	Trimethoprim capsules 1 × 100 mg	68	6 months
Juthani-Mehta et al,[22] 2016	RCT	Women in nursing home aged ≥65 years	2 cranberry capsules once per day (PAC = 36 mg)	92	2 placebo capsules once per day	93	360 days
Kontiokari et al,[23] 2001	RCT	Women who had UTI and not taking antimicrobial prophylaxis	Cranberry-lingonberry juice concentrate 50 ml/day	50	No. intervention	50	12 months
Stapleton et al,[18] 2012	RCT	Premenopausal women aged 18–45 years with a history of rUTI	Cranberry juice product 4 oz. and 8 oz	120	Placebo juice	56	6 months

RCT=randomized controlled trial; UTI=urinary tract infection; rUTI=recurrent UTI; PAC=proanthocyanidin; TMP–SMX=trimethoprim–sulfamethoxazole

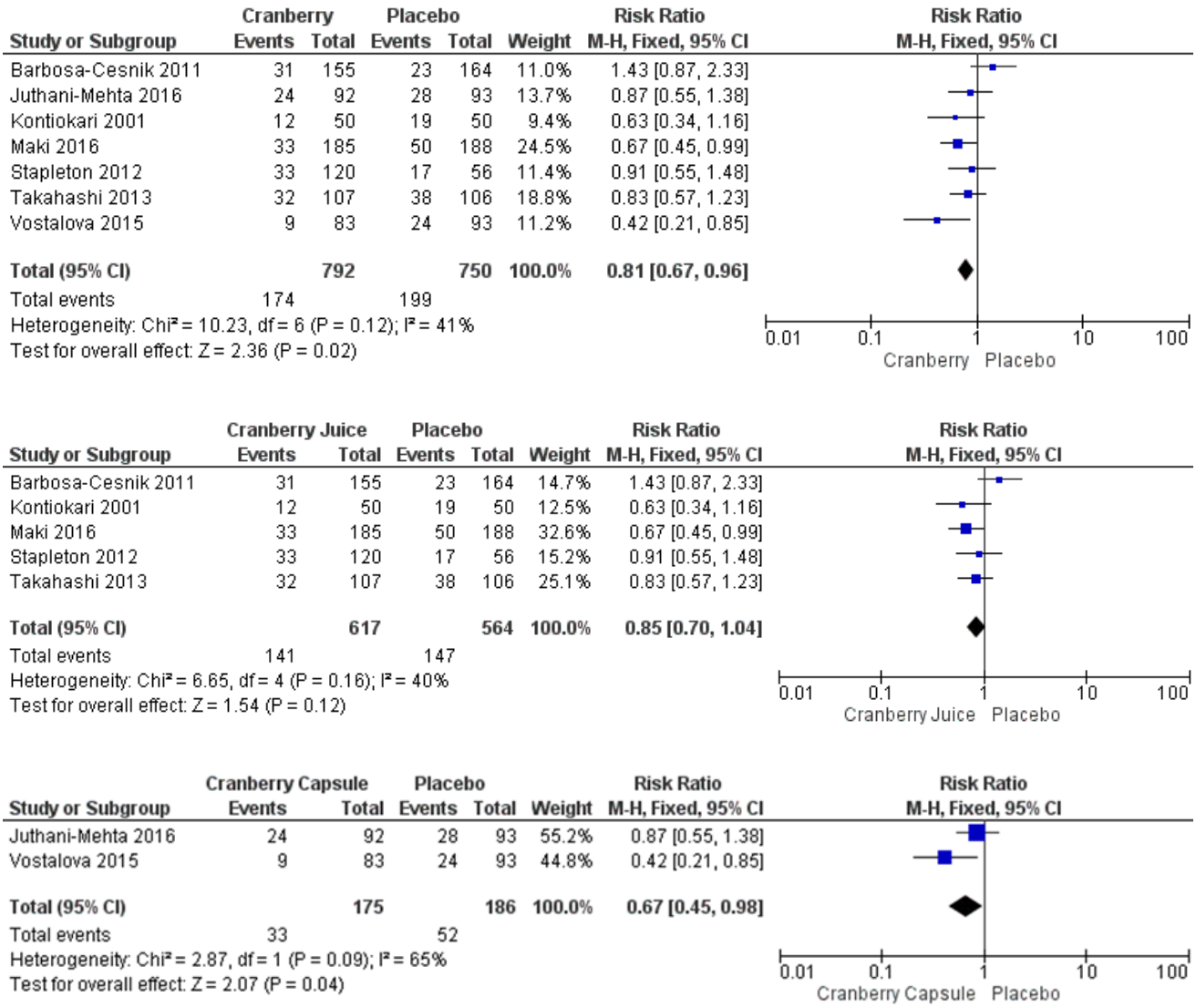

Figure 2. Forest plot for cranberry *versus* placebo

were five studies reporting incidences of rUTI after consuming either cranberry juice or placebo juice with a total of 1,181 participants (Figure 2). The combined analysis of these homogeneous studies ($p = 0.16$ and $I^2 = 40$) revealed a lower but nonsignificant incidence of rUTI in women consuming cranberry juice compared with women consuming placebo juice, with an RR of 0.85 (95% CI = 0.70–1.04).

Only two studies compared the effect of the consumption of cranberry capsules and placebo capsules with a total of 361 participants (Figure 2). These studies had a substantial heterogeneity, with $p = 0.09$ and $I^2 = 65\%$. The combined analysis using a fixed-effects model revealed a significantly lower incidence of rUTI in women consuming cranberry capsule compared with women consuming placebo, with an RR of 0.67 (95% CI = 0.45–0.98).

Based on the subgroup analysis, the risk of developing rUTI in women who consumed cranberry capsules *versus* placebo capsules was lower than that in women who consumed cranberry juice *versus* placebo juice, with the risk ratios being 0.67 and 0.85, respectively.

Cranberry *versus* antibiotic for rUTI treatment

Two studies compared the effect of cranberry capsules *versus* antibiotic (trimethoprim) with a total of 336 participants (Figure 3). These two studies reported a substantial heterogeneity, with $p = 0.08$ and $I^2 = 67\%$. Combined analysis using a fixed-effects model revealed a significant, 1.21 risk of developing rUTI (95% CI = 1.02–1.44) in women who consumed cranberry capsules compared with women who received the antibiotic (trimethoprim).

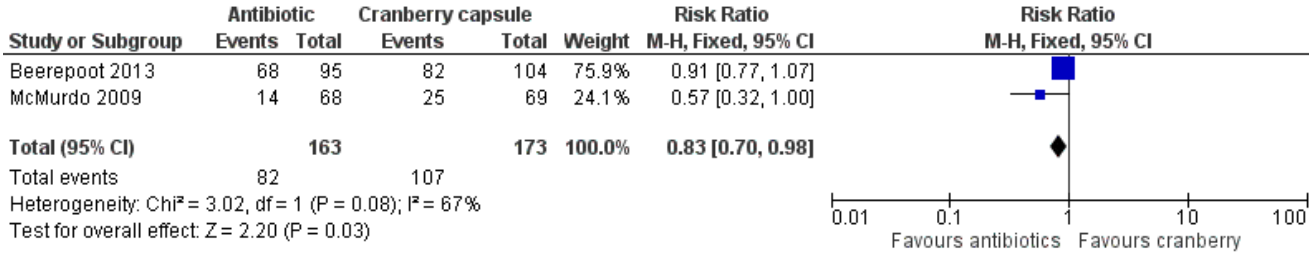

Figure 3. Forest plot for antibiotic *versus* cranberry capsules

Adverse events

Various adverse events, primarily minor, were reported among the studies. Stapleton et al[18] reported no serious adverse events in both study groups (cranberry juice *versus* placebo juice). Minor adverse events (e.g., gastrointestinal symptoms) were reported in 24.2% and 12.5% of the participants in the cranberry juice group and the placebo group, respectively (p = 0.07). McMurdo et al[19] demonstrated that itch/rash and loss to follow-up occurred more commonly in the trimethoprim group. Meanwhile, gastrointestinal symptoms were equally common in both groups (cranberry capsule and trimethoprim). Other adverse events were comparable between groups. Furthermore, Beerepoot et al[14] reported minor adverse effects (rash and gastrointestinal symptoms) with no significant differences between the TMP–SMX and the cranberry groups. In the TMP–SMX group, one subject experienced a severe adverse event (Stevens-Johnson syndrome). Therefore, she was withdrawn from the study. In contrast, there were no severe adverse events in the cranberry group.

Adherence

Adherence was determined based on the quantity of capsules ingested divided by the quantity of capsules that should have been ingested within each subject's duration of study. Among two studies, all the subjects had a good level of adherence. The study of Stapleton et al[18] reported that the mean monthly dose adherence was 90.3% in the placebo group and 91.8% in the cranberry group. Another study by McMurdo et al[19] also demonstrated good adherence in both groups, with a median value of 99% in the cranberry group and 100% in the trimethoprim group.

DISCUSSION

Cranberry consumption was associated with a significantly lower incidence of rUTI, as indicated by the evidence derived in this study. Several studies have suggested that cranberry effectively prevented UTI due to its acidity. However, this theory was contradicted by further studies, which found that the acidity of urine was increased only for a short period of time after cranberry consumption. Therefore, it may not prevent UTI effectively. Other studies have reported that fructose, one of the cranberry ingredients, could effectively inhibit bacterial adherence to various cells, especially type-1 fimbriated *E. coli*. However, there is a lack of clinical evidence regarding the correlation between fructose and UTI. Recently, it has been shown that cranberry proanthocyanidin (PAC), especially the A-type, could prevent UTI by avoiding the attachment of *E. coli* to some urogenital cell types. Gupta et al[20] explained that PAC could inhibit *E. coli* adherence to relevant model systems of primary cultured bladder and vaginal epithelial cells.

In this meta-analysis, there were five additional studies (Stapleton et al,[18] 2012, Takahashi et al,[21] 2013, Vostalova et al,[17] 2015, Juthani-Mehta et al,[22] and Maki et al,[16] 2016) besides two articles used in the final review (Kontiokari et al,[23] 2001 and Barbosa-Cesnik et al,[15] 2011). Two studies included in the previous review were not included in this review due to incompatibility with the study design. In contrast to the study reported by Jepson et al[12] in 2012, this study demonstrated a statistically significantly lower incidence of rUTI in women who consumed cranberry (all forms) than that in women who received placebo (RR = 0.81, 95% CI = 0.67–0.96), with a moderate heterogeneity (I^2 = 41%) compared to a higher heterogeneity in the final review (I^2 = 65%). The reason for the heterogeneity in this review is due to the inclusion of the study of Barbosa-Cesnik et al,[15] 2011 which had a larger sample size, a different terminology of UTI, and different results as described by Jepson et al.[12]

Results were varied among the subgroup analyses in terms of the cranberry form. In the

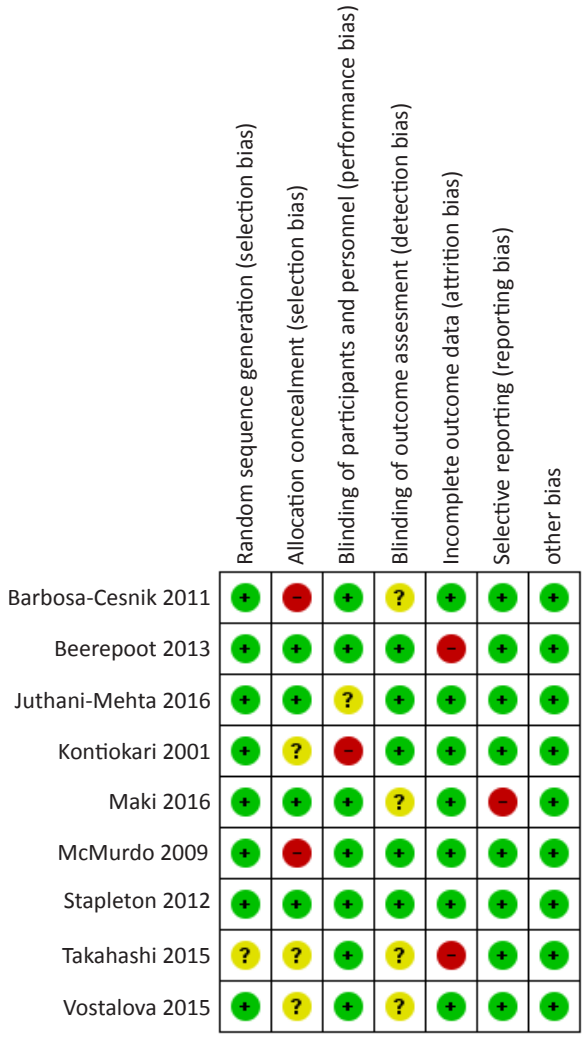

Figure 4. Risk-of-bias summary

cranberry juice group, the combined analysis revealed a lower but nonsignificant incidence of rUTI (RR = 0.85; 95% CI = 0.70–1.04). In the cranberry capsule analysis, with two studies comparing the treatment with the placebo group, there was a substantial heterogeneity (p = 0.09, I^2 = 65%). Consumption of cranberry capsules, unlike juice, was associated with a statistically significantly lower incidence of rUTI (RR = 0.67, 95% CI = 0.45–0.98).

The subgroup analysis showed that cranberry capsules had a better efficacy in preventing rUTI than the juice form. However, this result may be biased due to the different cranberry composition inside capsules and juices. Cranberry itself is primarily composed of water and a complex combination of organic acids, vitamin C, flavonoids, anthocyanidins, catechins, and triterpenoids.[24] However, each study in this review had its own cranberry form composition, especially in terms of the concentration of PAC. The different composition of other contents in cranberry capsules and juice may lead to different effects on the prevention of rUTI. In the juice, but not capsules, there might be a certain process of production and mixture of other components such as sugar, which may inhibit the effectiveness of other components. In addition, in this study, cranberry juice consumption was associated with a higher rUTI relative risk (RR = 0.85) than that of the consumption of capsules (RR = 0.67), with more acidity (pure cranberry juice has a pH <2.5 even with sweeteners). This juice also has to be consumed just before or 2 hours after meals and the patient has to drink plenty of water.[25]

There was limited evidence regarding the comparison of cranberry capsules with the antibiotic (trimethoprim) in terms of rUTI prevention. Only two studies were available. Consumption of cranberry capsules was associated with a higher relative risk than that of the antibiotic in terms of rUTI prevention (RR = 1.21; 95% CI = 1.02–1.44). A study by Bosmans et al[13] stated that the costs after 12 months in the cranberry group were significantly higher than those in the trimethoprim group (mean difference €249, 95% CI = 70–516). However, cranberry capsules had an advantage in terms of a lower risk of adverse events and antibiotic resistance.[13] Thus, even though cranberry had a lesser prophylaxis effect than trimethoprim, it had lower side effects.

Quality of the evidence and potential bias in the review process

All studies analyzed in this meta-analysis were RCTs. Based on this observation, no significant bias was found (Figure 4). One study had an attrition bias due to a large number of participants who were randomized but not included in the outcome analysis.[21] Another study had high loss to follow-up number.[14] A further limitation is the small sample size of most of the studies; three studies did not have enough sample. Therefore, this resulted in a lack of power to detect a realistic significant difference between the treatment groups. Study appraisal and data extraction were done independently by two authors without financial interest or any bias.

Conclusions

Overall, most of the patients had a good level of adherence to cranberry consumption. Cranberry consumption was significantly associated with

a significant lower incidence of rUTI compared with placebo. On the other hand, antibiotics were associated with a greater efficacy than cranberry but had a higher risk of adverse events. In terms of the preparation, cranberry capsules were more effective than juice to be given to patients. Some minor adverse events such as gastrointestinal symptoms and rashes must also be monitored and informed before cranberry administration.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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