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Research Article

Cranberry Extract for Preventing Recurrent Urinary Tract Infections: An Outcome-Specific Meta-Analysis of Prospective Trials

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Abstract

Background: Urinary tract infection (UTI) is one of the most common bacterial infections, representing enormous healthcare-cost and morbidity burdens. Though cranberries have long been used to prevent recurrent UTI (r-UTI), extant evidence is inconsistent. Potentials reasons for inconsistency include using different cranberry preparations (juice versus tablet/capsule), heterogenous populations, and outcome definition. Importantly, juice hardly a feasible long-term therapeutic option and there are no meta-analyses specifically examining tablet/capsule form of cranberry. We conducted an updated meta-analysis to address these inconsistencies.

Methods: MEDLINE was systematically searched for, i) placebo-controlled clinical trials, ii) restricted to adults, iii) exclusively investigating cranberry extract in tablet/capsule form to prevent r-UTI, and iv) clearly reporting incidence of any of the three outcomes (detailed subsequently) in treatment and placebo groups. Three outcome

measures, i.e culture-confirmed UTI, asymptomatic pyuria/bacteriuria, and symptomatic UTI were meta-analyzed separately.

Results: 15 RCTs met inclusion criteria. Ten trials reported culture-confirmed UTI, seven reported asymptomatic pyuria/bacteriuria, and 5 trials reported symptomatic but not culture-confirmed UTI as primary outcome, yielding twelve (n=2391 subjects), ten (n=2565 urine cultures), and seven (n=1325 subjects) independent cohorts, respectively. Meta-analysis revealed a 30% reduced risk of culture-confirmed UTI (pooled RR 0.70, 95% CI 0.54, 0.91; I^2=59%), 23% reduction in asymptomatic bacteriuria/pyuria (pooled RR 0.77, 95% CI 0.69, 0.86, I^2=75%), and 14% reduction in symptomatic UTI (RR 0.86, 95% CI 0.75, 0.98; I^2=48%). Excluding low-risk patients and those with neurogenic bladder having indwelling/intermittent catheterization reduced heterogeneity among culture-confirmed UTI trials revealing baseline risk profile of patients is a significant factor contributing to heterogeneity in extant literature. Funnel plot analysis did not reveal significant publication bias.

Discussion: Cranberry extract in capsule/tablet form reduces risk of r-UTI in those with a history of r-UTI, but not in those without such history, or those using indwelling or intermittent catheterization. Major limitation of available data was significant heterogeneity, though without evidence of publication bias.

Keywords: Urinary tract infection

1. Introduction

Urinary tract infections (UTIs) are one of the most common bacterial infections, amounting to >5 million office visits, over 1.5 million emergency department visits, and almost 400,000 hospital admissions, costing ≈$2.8 billion in the US alone [1, 2]. Much more common in women, 50-60% of all women experience a UTI in their lifetime, with 20-30% of those suffering recurrence within 6 months [3]. On a population basis, incidence of recurrent UTI (r-UTI) increases from 100/100,000 women 18-34 years old to 189/100,000 women aged 55-64 years [4]. Undoubtedly, r-UTI represents a significant individual and societal burden, both in cost and morbidity. Though antibiotic prophylaxis against r-UTI is effective, it is costly, comes with risk of adverse events, and raises legitimate concerns regarding anti-microbial resistance among uropathogens [5]. Hence, non-antimicrobial prophylaxis against r-UTI remains a topic of avid research. Cranberries have been used for over a century to prevent and treat UTIs. Acidification of urine, based on increased urinary hippuric acid secretion was long thought to mediate this benefit. However, combined with increasing awareness of bacterial adhesion in pathogenesis of UTI, in vitro studies in the 1980s revealed that cranberries have significant anti-adhesion properties [6, 7] Recently, anti-adhesion properties of cranberries have been attributed to plant polyphenols called proanthocyanidins (PACs), present in high concentrations in cranberries [8–10]. Numerous clinical trials over the last two decades have investigated the impact of cranberries in preventing r-UTIs. Unfortunately, inconsistent findings have resulted in conflicting conclusions and recommendations [11]. Multiple meta-analyses have frustratingly also come to conflicting conclusions [5, 12-15]. The most recent comprehensive meta-analysis was performed almost a decade ago, and concluded cranberry juice to

be ineffective in preventing r-UTIs [13]. Several prospective studies since have reported outcomes with cranberry extract in tablet/capsule form, hence the need for an updated analysis. Apart from inconsistent findings, admittedly due to heterogeneity among individual studies themselves, previous meta-analyses have suffered methodologic problems.

Firstly, all of them have included studies using cranberry in any form i.e juice or tablet, obtaining pooled outcomes with "cranberry product". This is problematic because bioavailability of plant flavonoids including anthocyanins is significantly influenced by the specific food matrix and chemical/heat/mechanical processing [16]. Hence, bioactivity of cranberry extract may well differ significantly from cranberry juice, and pooling these two interventions would skew results of a meta-analysis if one is ineffective or significantly different in efficacy from the other. Distinguishing between efficacy of the two cranberry formulations is critical because juice, even if beneficial, is hardly a viable therapeutic option due to high cost, well-known unpalatability amply demonstrated by a high attrition rates in several trials [15, 17, 18] and adverse effects of excess fluid and/or caloric intake that inevitably accompanies juice consumption, for example in diabetics and those with hypervolemic states. Moreover, there is inherent bias in cranberry juice studies, since most of these have used "placebo" juice as control, either flavored water or other fruit juices. This is problematic since hydration *per se* reduces UTI risk, making these studies essentially comparisons of two interventions, rather than true-placebo controlled trials. Given expected benefit in "placebo" groups from hydration, benefit of cranberry juice is likely to be muted. On the other hand, cranberry tablet/capsule trials have used true inert placebo as comparator. Hence, pooling trials using the two formulations risks distorting pooled effects in a meta-analysis. A second major issue with previous meta-analyses is pooling studies measuring diverse outcomes, i.e culture-confirmed UTI, asymptomatic bacteriuria/pyuria, or symptoms alone. Obviously, UTI definition majorly impacts incidence, usually higher defined based on symptoms alone rather than confirmed by urine cultures. Obviously, variability in incidence due to differing definitions *per se* will result in variable effect sizes and risk introducing avoidable heterogeneity in a meta-analysis, not to mention impact on the direction of pooled results. The "gold-standard" of diagnosing a UTI is positive urine cultures in a patient with symptoms consistent with a UTI, making this specific outcome of primary importance. Though it could be argued that treatment decisions in most uncomplicated UTIs are based on symptoms alone, from a scientific stand-point, the effects of a novel preventative must first be confirmed using a "gold-standard" definition. Hence, the efficacy of the only viable cranberry preparation i.e extract in tablet/capsule form, in modifying both culture-confirmed and symptomatic UTI is of interest. To address these issues, we conducted a meta-analysis limited to studies investigating the role of cranberry extract in preventing r-UTI, stratified by outcome definition *a priori*.

2. Methods

2.1 Study identification

We searched PUBMED/MEDLINE for clinical trials using terms "cranberry", "cranberries", or "cranberry extract" AND "urinary tract infection", "UTI", "cystitis", "pyuria", "bacteriuria", or "dysuria". We did not search conference abstracts or clinical trial registries. Bibliographies of published systematic reviews and individual studies were also

searched. We included, i) prospective randomized controlled trials (parallel group or cross-over design), ii) restricted to adults, iii) comparing cranberry extract in tablet/capsule form to placebo or non-placebo control, and iv) clearly defining and reporting each or any of the three end-points in treatment and placebo/control groups. Studies recruiting subjects with neurologic injury/disease, and hence indwelling catheters or undergoing intermittent catheterization, were included. We excluded trials i) using cranberry juice, ii) with treatment duration <30 days, iii) those where incidence of outcome in treatment and placebo groups were not reported as participants with ≥1 UTI (with culture-confirmed UTI or symptomatic UTI as outcome) or number of positive urine cultures (with pyuria/bacteriuria as outcome), iv) studies with active control (antibiotics/other experimental therapies), and finally, v) studies including cranberry combined with another fruit/natural product.

2.2 Study selection, data extraction, and quality assessment

After eliminating duplicates, titles and abstracts of remaining studies were scanned to identify potential candidates. Full-text manuscripts of studies, thus identified, were assessed per the specified inclusion/exclusion criteria for eligibility. Conflicts or differences of opinion were settled by consensus among all authors. Five authors independently extracted data from eligible studies into a pre-designed spreadsheet. Extracted data included study design (parallel/cross-over), duration (months), dosing frequency, population characteristics, outcome definition, and outcome incidence, among others. Studies were sub-divided by one of three outcomes, 1) culture-confirmed UTI, expressed as incidence of ≥1 UTI, 2) asymptomatic pyuria and/or bacteriuria, expressed as number of positive urine cultures, and 3) symptomatic UTI, expressed as for culture-confirmed UTI. The Cochrane risk of bias tool was used to assess the risk of bias for each included study, and graded as "high-risk", "low-risk", or "unclear risk" for each of, 1) random sequence generation, 2) allocation concealment, 3) blinding, 4) incomplete outcomes data, 5) selective reporting, and 6) other bias [19]. Risk of bias was assessed by two authors (HG, JH) and any conflicts were settled by group consensus

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2.3 Data analysis

Included studies were divided by outcome definition into three categories, i.e. culture-confirmed UTI, pyuria and/or bacteriuria, and symptomatic UTI. These three outcomes were analyzed separately. Some studies had multiple parallel arms, either based on population characteristics (low-risk versus high-risk), or based on cranberry extract dosing (low-dose versus high-dose). In these cases, all arms were analyzed as discreet cohorts. Individual study effect sizes were computed as risk-ratios (RRs) with 95% confidence intervals. Heterogeneity was tested using the I^2 statistic, where $I^2 \geq 50\%$ indicated significant heterogeneity, and the chi-square test, with $P \leq 0.05$ indicating significant heterogeneity. Weighted pooled effect-size estimates were obtained using random-effects model (DerSimonian-Laird method) when either test indicated heterogeneity. Fixed-effects (Mantel-Haenszel method) summary estimates were obtained in case of low heterogeneity (I^2 <50%, and P>0.05). Meta-analysis was performed using Review Manager (RevMan), version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Publication bias was assessed using funnel plots. Funnel plot asymmetry was assessed using Egger's test and Kendall's rank correlation test. In case of significant funnel plot asymmetry, we planned on

considering fill and trim adjustment to funnel plots. Case-wise diagnostics were performed by visual inspection of the funnel plots, radial plots, and by influence measures statistics, to identify outliers contributing to heterogeneity. Among influence measures, we were largely interested in Cook's distance, which is the distance between effect-size with the study included compared to when it is excluded, hence being a measure of how strongly each study influences the overall pooled effect size. Cook's distance <1.0 is usually accepted as cut-off below which any single study is not deemed to have a predominant influence. The second measurement of interest was the covariance ratio, which indicates (when <1.0) whether removing the study would lead to a more precise effect-size estimate. Heterogeneity diagnostics and funnel plot analysis were performed using the statistical software JASP (JASP Team (2020). JASP (Version 0.12.2) [Computer software].

3. Results

3.1 Study characteristics

Fifteen studies met inclusion criteria for quantitative synthesis [20-34]. PRISMA flow-diagram of the literature search is depicted in Figure 1. Study characteristics are summarized in Table 1, stratified by outcome. Briefly, 5 studies reported symptomatic UTI (not culture-confirmed) as the primary outcome [26-28, 32, 33], yielding 7 comparison cohorts, since one study (Caljouw et al) had 3 intervention arms based on baseline UTI risk, i.e. low risk (no history of recurrent UTI and non-diabetic), high-risk (diabetics or history of r-UTI, but not catheterized) and catheterized patients. Ten studies reported culture-confirmed symptomatic UTI as the primary outcome, yielding 12 comparison groups (Caljouw et al having three parallel groups, as above) [21, 23-25, 27-31, 34]. Seven studies reported incidence of asymptomatic pyuria and/or bacteriuria, yielding 10 comparison groups (Sengupta et al having two independent PAC-dose groups, and Bianco et al having three independent PAC-dose groups) [20, 22, 23, 26, 30-32]. Five trials exclusively enrolled patients with neuropathic bladder, three including patients with spinal cord injury [26, 30, 33], and two including patients with multiple sclerosis [29, 34]. The SINBA trial (Lee 2007) had three intervention arms besides placebo, i.e. cranberry+methenamine-hippurate, cranberry alone, and methenamine-hippurate alone [33]. For our analysis, we only included the cranberry alone versus placebo groups. Only one trial was cross-over [30], the rest being parallel design. Figure 2 summarizes individual study quality and risk of bias assessment. Just over half the studies (8/15) were well-randomized and double-blinded, with the rest not clearly reporting their randomization process. Most studies had low risk of attrition bias (<20% attrition).

3.2 Quantitative synthesis

3.2.1 Impact of cranberry extract on culture-confirmed UTI: There were 2391 subjects across 10 trials (totaling 12 cohorts) reporting culture-confirmed symptomatic UTI, 1174 in cranberry group and 1217 in placebo (PBO) group. There was significant heterogeneity (I^2=59%, P=0.005). Pooled random-effects summary estimates revealed a significant reduction in risk of r-UTI with cranberry extract versus PBO (RR: 0.70, 95% CI: 0.54, 0.91, p=0.008, figure 3, upper panel). Funnel plot analysis (Egger's test: z=0.080, p=0.936; Kendall's rank correlation test: τ=-0.061, p=0.841) revealed no evidence of significant publication bias (figure 5, upper panel, table S1), hence lack of need for trim-fill analysis. Influence measures analysis did not reveal any one study having undue influence on

overall effect size (Cook's distance <1.0 for all studies, table S2). This was also evident with sensitivity analysis, performed using the leave-one-out method, which revealed stable effect sizes (figure 4, upper panel). Caljouw et al [27] (catheterized cohort), and Singh et al [23] had covariance ratios <1.0, and were also outliers on visual inspection of the funnel plots, indicating that omitting these studies would likely lead to more precise effect-size estimates.

Indeed, repeating the analysis after excluding these two cohorts revealed persistent benefit from cranberry extract (RR: 0.72, 95% CI: 0.57, 0.90, p=0.004), this time with low heterogeneity (I^2=36%, P=0.12). Subgroup analysis provided further notable insights as to causes of heterogeneity among the literature (Table 2). Firstly, benefit of cranberry extract seemed limited to patients at high-risk of UTI, with no benefit in low-risk patients, i.e those without history of r-UTI. Similary, neither did there appear to be benefit in patients at an extremely high-risk, i.e. those with neurogenic bladder and/or having indwelling or chronic intermittent catheterization. Hence, in the middle of the risk spectrum, i.e those with history of r-UTI without neurogenic bladder and/or bladder catheterization, the benefit of cranberry extract not only became stronger (RR: 0.54, 95% CI: 0.39, 0.74), there also was a significant drop in heterogeneity (I^2 = 42%, P=0.14).

Hence, further sub-group analyses were performed excluding trials limited to these two populations i.e low-risk of r-UTI and catheterized. Initially, cranberry extract seemed to exert no benefit among longer (≥6-month) studies, in contrast to studies <6 months. However, excluding catheterized/neurogenic bladder and low-risk cohorts revealed benefit regardless of study duration. Similarly, once daily versus more frequent dosing had no impact on benefit when catheterized and low-risk patients were excluded. Finally, studies exclusively recruiting females showed a significant benefit with cranberry extract, with no heterogeneity among studies. Pooling studies recruiting both genders (n=6) revealed no benefit with cranberry extract. However, 3 of these included catheterized or low-risk patients. Excluding these cohorts revealed a significant benefit in bi-gender studies, though there seemed to be some attenuation of effect, and significant heterogeneity. Notably, there were no studies exclusively enrolling males, hence the last sub-group comparison was essentially between studies exclusive to females, and studies enrolling both genders. Finally, only two trials recruited healthy community-dwelling females, totaling 276 patients (133 cranberry versus 143 PBO) [24, 25], again demonstrating significant benefit with cranberry extract (RR: 0.49, 95% CI: 0.29, 0.80; p=0.005, I^2=0%, p=0.57).

3.2.2 Impact of cranberry extract on asymptomatic bacteriuria and/or pyuria: All studies in this group collected multiple urine samples per subject throughout the study period, reporting proportions of positive urine cultures in treatment and placebo arms. In total, 2565 urine samples were collected across 7 trials (totaling 10 cohorts), 1319 in cranberry group and 1246 in placebo group. There was significant heterogeneity among studies (I^2=75%, p<0.0001). Pooled summary estimates (figure 3, middle panel) revealed a significant benefit with cranberry versus placebo in reducing asymptomatic pyuria/bacteriuria (RR: 0.77, 95% CI: 0.69, 0.86, p<0.0001). Funnel lot analysis did not indicate presence of significant publication bias (Egger's test: z=-1.356, p=0.175;

Kendall's τ=-0.333, P=0.216) as noted in figure 5, middle panel, and table S1. Influence measures analysis revealed Singh et al with a Cook's distance of >1.0, also evident as an outlier on visual inspection of the funnel plot, and radial plot indicating significant influence of this one study of pooled effect size. Additionally, Singh et al [23] also had a covariance ratio <1.0. Not surprisingly, excluding this study resulted in attenuated (but still statistically significant) effect size among remaining 5 trials (RR: 0.87, 95%CI: 0.76, 0.99, p=0.04). Moreover, excluding Singh et al resulted in elimination of heterogeneity (I^2=4%, P=0.39), indicating this one study driving most of the observed pooled effect-size as well as most of the heterogeneity. Since the study by Ledda et al was also an outlier on radial and funnel plot inspection, along with a covariance ratio just under 1.0, we repeated the analysis excluding these two studies [23, 32]. This time, effect size was further attenuated, now remaining borderline significant, with elimination of heterogeneity (RR 0.89, 95% CI 0.79-1.01, p=0.06, I^2 = 0%, P = 0.99).

Sensitivity analysis revealed stable effect estimates (figure 4, middle panel). Notably, the trial by Singh et al was generally low-quality-with poorly-defined outcomes, and selective reporting, while the study by Leda et al was a small (n=22 in each group) pilot registry study where both intervention and control groups received "lifestyle advice". Two trials exclusively enrolled patients with neurogenic bladder due to spinal cord injury [26, 30]. There was no benefit with cranberry extract in this subgroup (RR: 0.87, 95% CI: 0.65, 1.15, p=0.32) and no heterogeneity (I^2=0%, P=0.32). On the other hand, there was significant RR-reduction in non-catheterized and non-neurologic injury patients (RR: 0.75, 95% CI: 0.67, 0.84, p<0.00001), but with significant heterogeneity (I^2=80%, P<0.0001). Two trials were conducted in nursing home dwelling elderly females [20, 31] totaling 1389 patients (683 cranberry versus 706 PBO), revealing reduced risk with cranberry extract, but with high heterogeneity (RR: 0.75, 95% CI: 0.66-0.85, p<0.0001, I^2=86%, P<0.0001). Finally, three trials conducted in young healthy females [22, 23, 32], totaling 540 subjects (306 cranberry versus 234 PBO), also revealed significant benefit with cranberry extract (RR 0.56, 95% CI: 0.46-0.67, p<0.0001, I^2=82%, P=0.0007).

3.2.3 Impact of cranberry extract on symptomatic, non-culture confirmed UTI: Five trials yielded 7 cohorts, totaling 1325 patients, 658 in cranberry and 667 in PBO groups. There was borderline heterogeneity (I^2=48%, P=0.07). Pooled estimates (figure 3, lower panel) revealed significant benefit with cranberry extract (RR: 0.86, 95% CI: 0.75, 0.98, p=0.03). Funnel plot analysis again revealed no evidence of publication bias (Eggers test: z=-0.007, p = 0.995; Kendall's τ = 0.048, p=1.000), though it is worth noting that these tests are generally deemed underpowered to detect publication bias with fewer than 10 studies (figure 5, lower panel, table S1). There were no clear outliers either on visual inspection of funnel plot or radial plot (figure 5, lower panel).

Results were unstable on sensitivity analysis (figure 4, lower panel). However, influence measures showed Caljouw [27] (low-risk cohort) and Foxman et al, [28] having a covariance ratio <1.0, indicating excluding these two studies could yield more precise results (table S1). Indeed, excluding these two studies yielded significant pooled effect size with elimination of heterogeneity (RR 0.83. 95% CI, 0.71-0.97, p=0.02, I^2 = 0%, P = 0.41). On sub-group analysis, cranberry extract seemed to benefit non-catheterized patients with history of r-UTI (RR: 0.75, 95% CI: 0.61, 0.91,

p=0.004) with low heterogeneity (I^2=0%, P=0.58), though there were only two trials in this sub-group, totaling 464 subjects (226 cranberry vs 238 PBO) [27, 32]. There was no benefit in catheterized/neurogenic bladder patients (RR: 0.84, 95% CI: 0.67, 1.04, p=0.11).

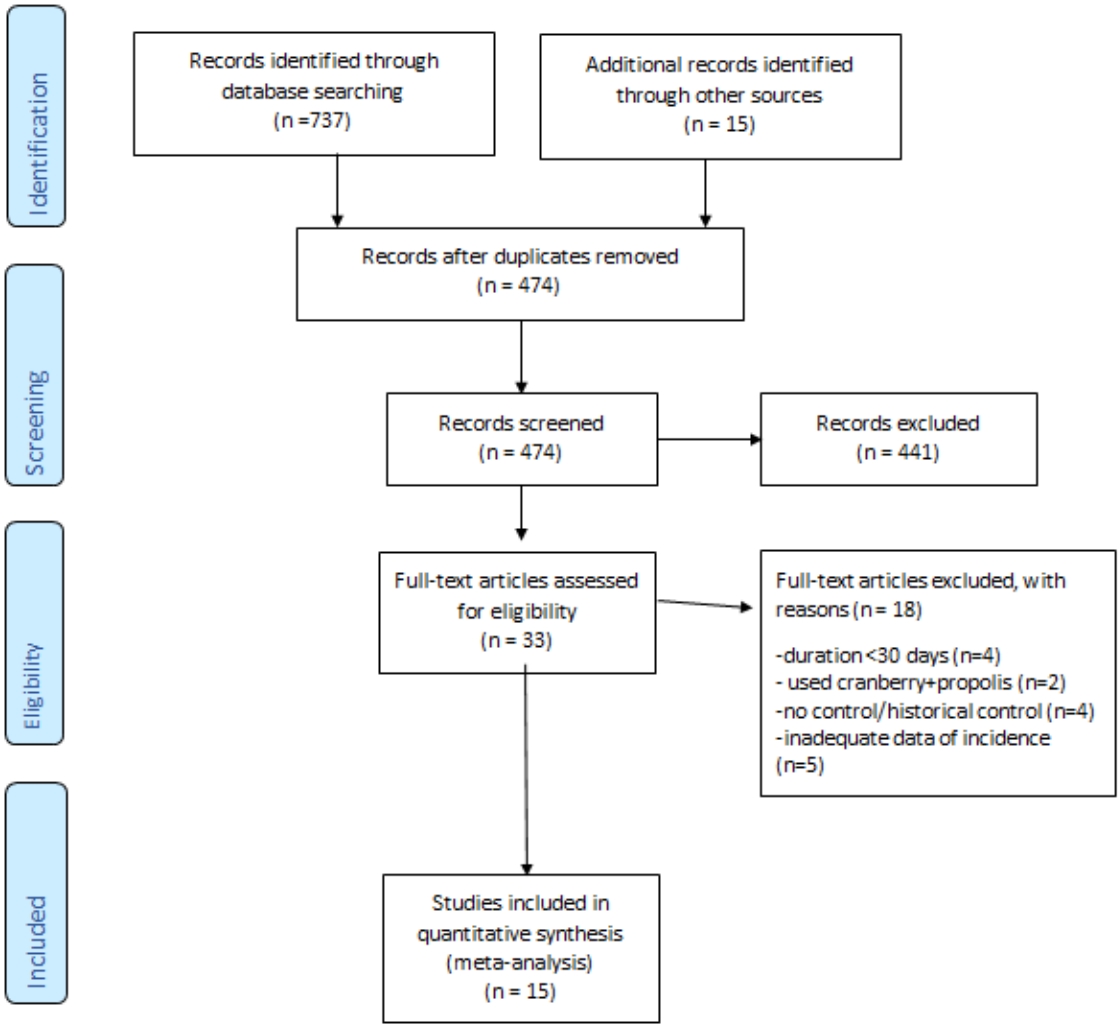

Figure 1: Summary of literature search.

First author, year	Sample size (Rx/PBO)	Design	Duration (Months)	Setting	Patient characteristics	Doses/day	Daily PAC dose (mg)	Placebo used
Symptomatic UTI (not confirmed by urine cultures)								
Waites, 2003[26]	48 (26/22)	Parallel RCT (2-arm)	6	Community	SCI with neuropathic bladder (M+F)	QD	NR (Brand no longer existent)	Lactose capsule
Lee, 2007[33]	155 (78/77)	Parallel RCT (2-arm)	6	Community	SCI with neuropathic bladder (M+F)	BID	NR (Brand/manufac-turer not reported)	NR
Caljouw, 2014[27]	928 (458/470)	Parallel RCT (4-arm)	12	LTC	Low risk, high risk without indwelling catheter, high risk with indwelling catheter (M+F)	BID	18	Cellulose microcrystal colored red with azorubin
Ledda, 2015[32]	44 (22/22)	Parallel RCT (2-arm)	2	Community	r-UTI (3 UTIs/year or 2 UTIs/6 months)	QD	36	Non-placebo control
Foxman, 2015[28]	160(80/80)	Parallel RCT (2-arm)	1.5	Community	≥18 y/o females undergoing gynecologic surgery	BID	NR (≈72 mg)	NR (supplied by sponsor)
Culture-confirmed symptomatic UTI								
McGuiness, 1997[34]	135 (62/73)	Parallel RCT (2-arm)	6	Community	MS with neurogenic bladder	QD	NR (No longer available by manufacturer)	Beetroot powder capsule

Stothers, 2002[24]	100 (50/50)	Parallel RCT (2-arm)	12	Community	Adult females with r-UTI (≥2/year)	BID	NR (Brand/manufacturer not reported)	NR
Hess, 2008[30]	47 (47/47)	Crossover	6	Community	SCI with neurogenic bladder	BID	NR (≈36 mg)	Rice flour tablet
Bonetta, 2012[21]	370 (186/184)	Parallel RCT (2-arm)	1.5	Community	Males undergoing radiation for prostate carcinoma	QD	60	Non-placebo control
Caljouw, 2014[27]	928 (458/470)	Parallel RCT (4-arm)	12	LTC	Low risk, high risk without indwelling catheter, high risk with indwelling catheter males and females	BID	18	Cellulose microcrystal colored red with azorubin
Gallien, 2014[29]	171 (82/89)	Parallel RCT (2-arm)	12	Community	MS with urinary disorders	BID	36	NR (matching powder)
Foxman, 2015[28]	160 (80/80)	Parallel RCT (2-arm)	1.5	Community	≥18 y/o females undergoing gynecologic surgery	BID	NR (≈72 mg)	NR (supplied by sponsor)
Vostalova, 2015[25]	176 (83/93)	Parallel RCT (2-arm)	6	Community	>18 y/o females with r-UTI (≥2 UTIs/year)	QD	2.8	maltodextrin, canola oil, sodium aluminium silicate, Red 40 Lake, Blue 1 Lake capsule

Juthani-Mehta, 2016[31]	185 (92/93)	Parallel RCT (2-arm)	12	LTC	>65 y/o females. r-UTI not required	QD	72	NR
Singh, 2016[23]	72 (36/36)	Parallel RCT (2-arm)	3	Community	Asymptomatic bacteriuria and/or r-UTI	BID	120	Lactobacillus capsule
Pyuria and bacteriuria								
Waites, 2003[26]	288 (156/132)	Parallel RCT (2-arm)	6	Community	SCI with neuropathic bladder	QD	NR	Lactose capsule
Hess, 2008[30]	282 (282/282)	Crossover	6	Community	SCI with neurogenic bladder	BID	NR (≈36 mg)	Rice flour tablet
Sengupta, 2011[22]	228 (176/52)	Parallel RCT (3-arm)	3	Community	18-40 y/o females with dysuria and frequency	BID	7.5/15	Non-placebo control
Bianco, 2012[20]	450 (222/228)	Parallel RCT (4-arm)	1	LTC	Females ≥ 65 y/o with r-UTI	QD	36/72/108	NR
Ledda, 2015[32]	44 (22/22)	Parallel RCT (2-arm)	2	Community	r-UTI (3 UTIs/year or 2 UTIs/6 months)	QD	36	Non-placebo control
Singh, 2016[23]	216 (108/108)	Parallel RCT (2-arm)	3	Community	≥18 y/o females with asymptomatic bacteriuria or r-UTI	QD	120	Lactobacillus capsule
Juthani-Mehta, 2016[31]	723 (353/370)	Parallel RCT (2-arm)	12	LTC	Females >65 years old. r-UTI not required	QD	72	NR

Table 1: Study characteristics of individual studies included in quantitative synthesis of the effect of cranberry extract in reducing r-UTIs.

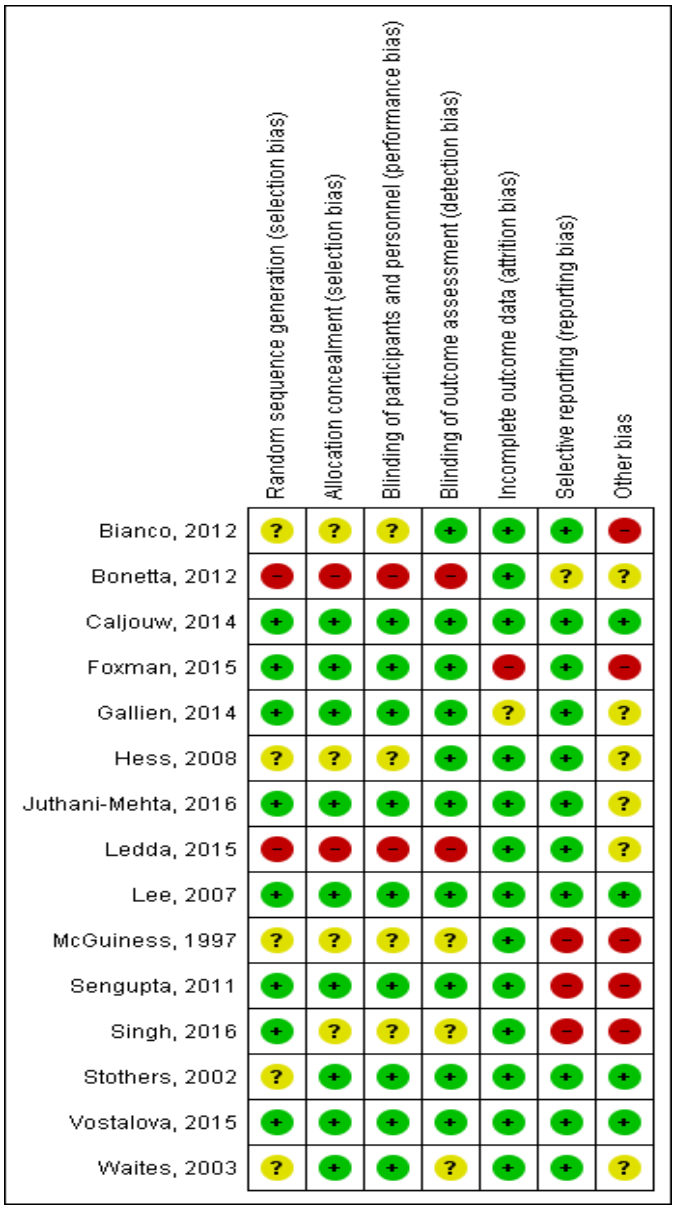

Figure 2: Risk of bias assessment.

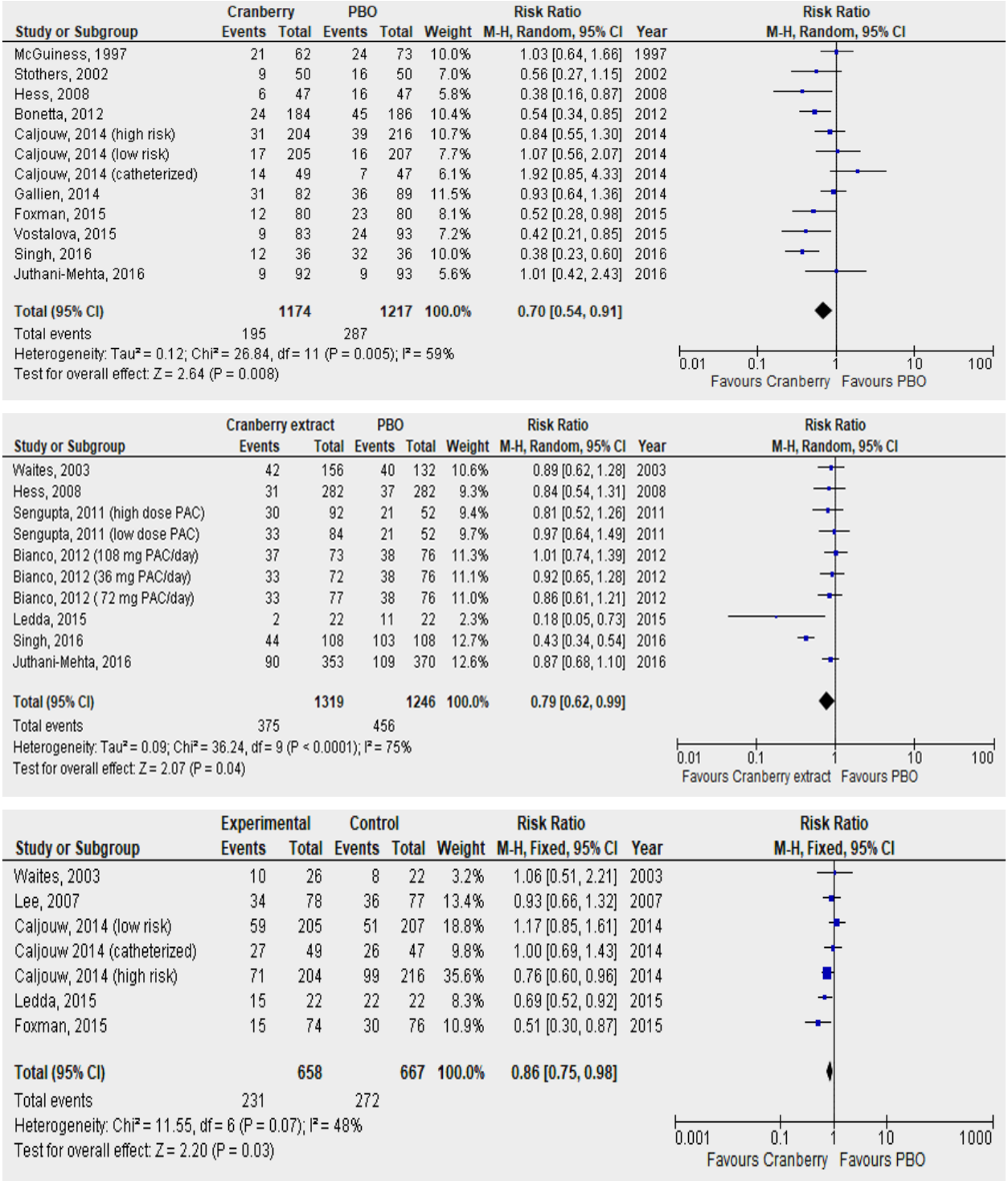

Figure 3: Forest plots depicting pooled relative risk (RR) of recurrent UTI after cranberry extract versus placebo for the three outcomes of culture-confirmed UTI (upper panel), asymptomatic pyuria and bacteriuria (middle panel) and symptomatic UTI (lower panel).

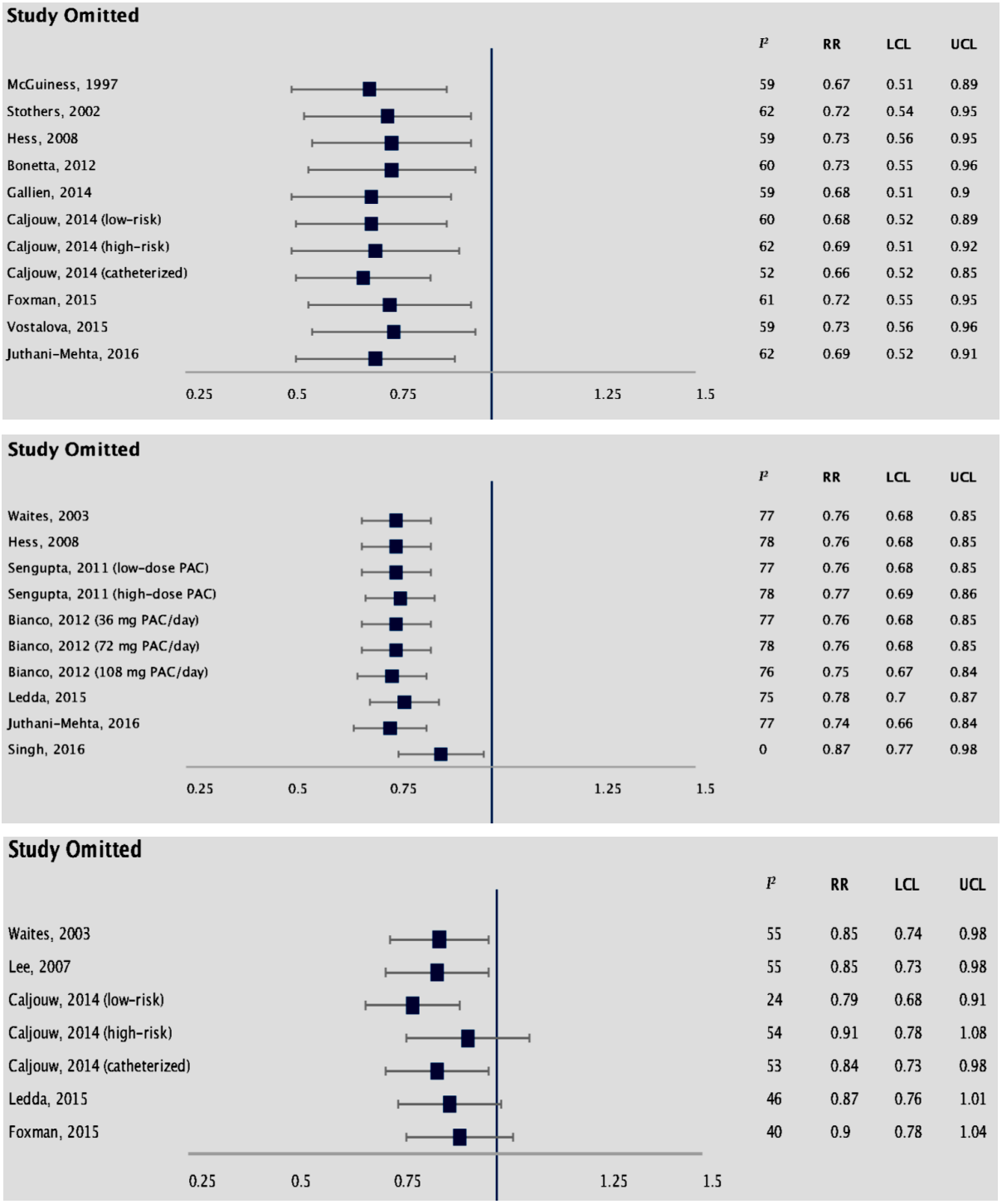

Figure 4: Sensitivity analysis depicting pooled effect sizes and heterogeneity on omitting one study at a time from meta-analysis of the three outcome definitions i.e culture-confirmed UTI (upper panel), asymptomatic pyuria and bacteriuria (middle panel), and symptomatic UTI (lower panel).

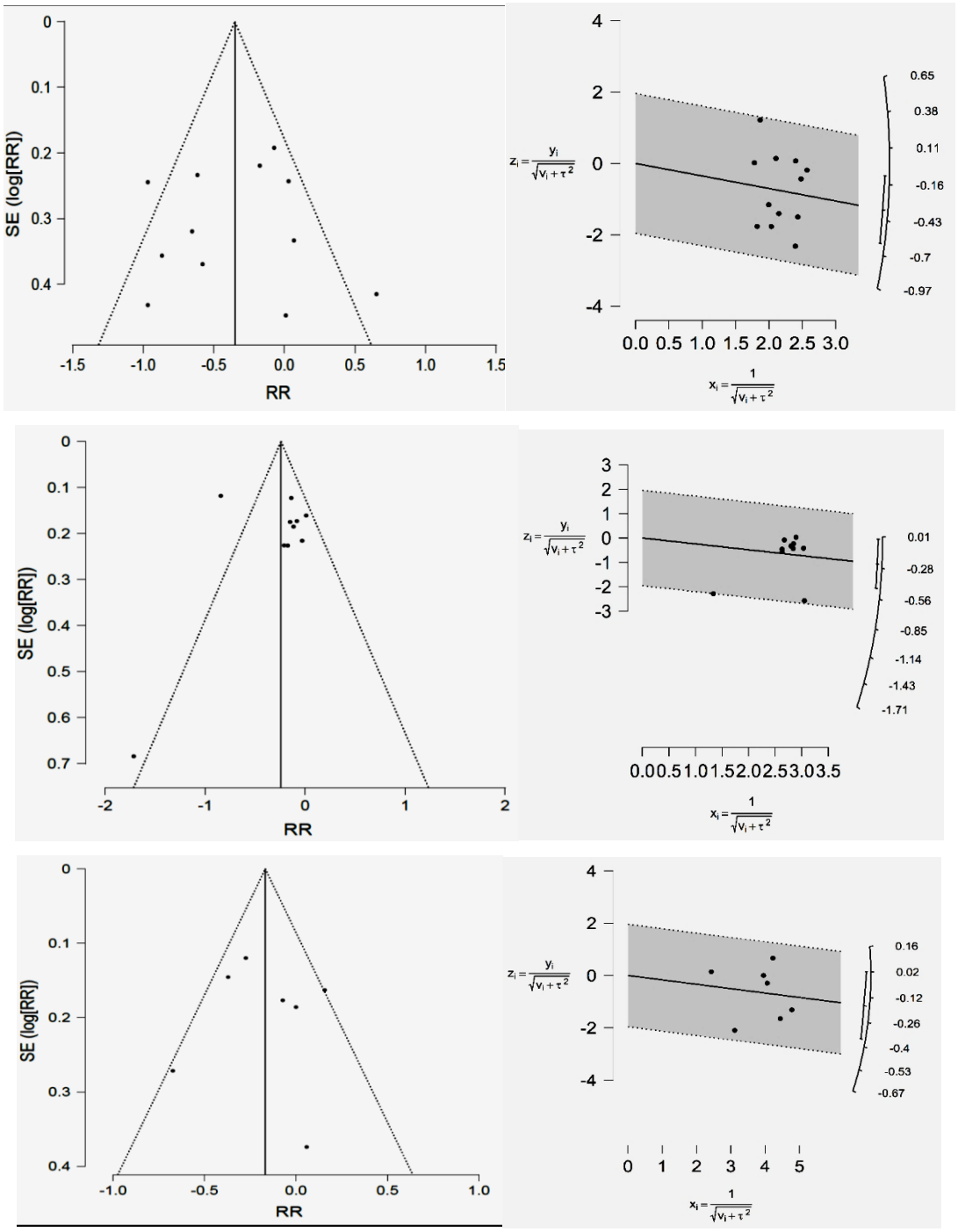

Figure 5: Funnel plots (upper-left, middle-left, and lower-left panels) and radial pots (upper-right, middle-right, and lower-right panels) for culture-confirmed UTI, asymptomatic pyuria/bacteriuria, and symptomatic UTI.

Subgroup analysis (Culture-confirmed UTI)	**Cohorts, n**	**References**	**Pooled cumulative UTI incidence**		**RR (95% CI)**	**Heterogeneity, I^2 (%)**
			Cranberry	**PBO**		
Overall	**12**	[21, 23–25, 27–31, 34]	**195/1174**	**287/1217**	**0.70 (0.54, 0.91)**	**59**
Baseline risk						
Very high risk (catheterized patients, neurogenic bladder)	5	[27–30, 34]	84/320	106/336	0.83 (0.54, 1.28)	62
High-risk (r-UTI, not catheterized)	5	[21, 23–25, 27]	85/557	156/581	0.54 (0.39, 0.74)	42
Low-risk (no ruti)	2	[27, 31]	26/297	25/300	1.05 (0.62, 1.78)	0
Study duration						
<6 months	3	[21, 23, 28]	48/300	100/302	0.47 (0.35, 0.63)	0
≥ 6 months	9	[24, 25, 27, 29–31, 34]	147/874	187/915	0.83 (0.64, 1.09)	43
≥ 6 months (excluding catheterized/low-risk)	4	[24, 25, 27, 31]	58/429	88/452	0.69 (0.48, 0.98)	20
Gender						
Females only	4	[24, 25, 28, 31]	39/305	72/316	0.56 (0.39, 0.80)	0
Females only (excluding catheterized/low-risk)	3	[24, 25, 31]	27/225	49/236	0.59 (0.37, 0.94)	15
Females+males	6	[21, 23, 27, 29, 30, 34]	156/869	215/901	0.76 (0.55, 1.06)	69
Females+males (excluding catheterized/low-risk)	3	[21, 23, 27]	49/287	87/299	0.51 (0.28, 0.94)	72
Dose frequency						
Once daily	4	[21, 25, 31, 34]	63/421	102/445	0.69 (0.44, 1.07)	54

Once daily excluding catheterized/low-risk	3	[21, 25, 31]	42/359	78/372	0.57 (0.38, 0.84)	17
> Once daily	8	[23, 24, 27–30]	132/753	185/772	0.71 (0.50, 1.01)	66
> Once daily excluding low-risk/catheterized	4	[21, 23, 24, 27]	76/474	132/488	0.56 (0.39, 0.81)	52
Risk of selection bias						
Low-risk	8	[23, 25, 27–29, 31]	135/831	186/861	0.75 (0.53, 1.07)	66
Low-risk excluding catheterized and low UTI risk	4	[23, 25, 27, 31]	61/415	104/438	0.59 (0.36-0.97)	65
High/unclear risk	4	[21, 24, 30, 34]	60/343	101/356	0.62 (0.41-0.95)	51

Table 2: Subgroup analysis of the effect of cranberry extract on risk of culture-confirmed UTI.

4. Discussion

We present an updated, outcome specific meta-analysis of cranberry extract for prevention of r-UTI. This is the first meta-analysis exclusive to what is the majorly feasible therapeutic formulation, i.e extract in capsule/tablet form. Key findings include, i) cranberry extract as tablet/capsule is effective in reducing risk of r-UTI with the gold-standard criterion of positive urine cultures in symptomatic patients, with ≈30% reduction in UTI risk, ii) cranberry extract is effective in reducing rates of asymptomatic pyuria/bacteriuria, as well as symptomatic UTI, iii) the benefit of cranberry extract seems restricted to those with history of r-UTI, but ineffective in those at low-risk (i.e. those without recurrent UTI) and in catheterized and/or neuropathic bladder patients. We found that the latter two populations revealed a persistent benefit regardless of outcome definition, and with significantly less heterogeneity. The lack of benefit in catheterized populations is important and not too difficult to explain. The anti-adhesion properties of PACs have largely been studied and demonstrated in gram-negative bacteria, more specifically *E. coli*. Since catheterized patients are at risk of UTI with a broader class of pathogens, including gram-positive bacteria, it may well be that these anti-adhesive properties fail in these patients. Moreover, the mechanism of catheter-associated UTI is complex, including bio-film formation on catheters, mucosal injury from the catheters, among others. Hence it may represent too over-whelming a risk, or a mechanism not modifiable by PACs. Our findings are all the more robust given that cranberry extract proved to be ineffective in this population regardless of outcome-definition. Furthermore, baseline population risk profile seems to drive much of the heterogeneity in extant literature. Indeed, heterogeneity was significantly attenuated when studies in populations at extremes of baseline risk

profile were excluded. A major drawback we encountered in the extant literature is significant publication bias, especially prominent among studies using asymptomatic pyuria/bacteriuria and symptomatic UTI as outcomes. Indeed, previous meta-analyses suffered significant heterogeneity and even conflicting conclusions because of three likely factors, i) pooling studies with different outcome definitions, ii) pooling studies in varied populations with regards to baseline risk profile, and/or c) pooling studies using both juice and cranberry extract. It is worth mentioning that we did not expressly test the last factor since excluded all juice studies. Briefly, there have been 4 meta-analyses in the last decade to examine the effect of cranberries in this context [13-15, 35]. Jepson et al reported a meta-analysis in 2012, predating almost two-thirds of trials included in our analysis [13]. Majority of included trials used cranberry juice, which as noted by the authors themselves at the time, is hardly a feasible long-term therapeutic option. They found no benefit of cranberry "product" in reducing UTI risk (RR 0.86, 0.71-1.04). No separate analysis by formulation was performed. A meta-analysis by Wang et al the same year included 10 studies (10 juice, 4 tablet/capsule), and found significant benefit with cranberry "product" [15]. On subgroup analysis, tablet/capsule group had no benefit (RR 0.79, 0.44-1.44) though cranberry juice seemed to lower UTI risk (RR 0.47, 0.30-0.72). Notably, three of the four tablet/capsule studies were limited to neuropathic bladder patients, a group that our findings suggest does not benefit from cranberry extract. Finally, subgroup analysis by outcome definition revealed cranberry product to lower risk of only symptomatic UTI and not culture-confirmed UTI, highlighting the role of outcome definition in introducing heterogeneity and indeed conflicting findings. Regardless, both these meta-analyses predated majority of trials included in the current meta-analysis.

More recently, Fu et al conducted a meta-analysis of 7 trials exclusive to healthy women [14]. Again, pooling studies using cranberry juice and tablet/capsule, they found no overall benefit. Interestingly, cranberry tablet/capsule subgroup revealed a benefit over juice (RR 0.79, 0.59-1.06 for juice versus 0.48, 0.29-0.79 for tablet/capsule), though based on only two trials using tablet/capsule. Using culture-confirmed UTI as outcome, there was no benefit with cranberry product (RR 0.71, 0.45-1.12), again pooling tablet/capsule and juice trials. There was no separate analysis by formulation for culture-confirmed UTI. In a larger meta-analysis, Luis et al pooled results from a broad set of studies conducted in all age groups including children, pregnant females, and those with neurogenic bladder [35]. Again, trials using both cranberry formulations and all outcome definitions were pooled, as were studies using non-placebo control (antibiotics, other probiotics, etc). Similar to our findings, though there was reduced UTI-risk overall (RR 0.68, 0.57-0.80), there was no benefit in catheterized subjects (RR 0.89, 0.68-1.17). They also found no benefit in young adults (18-35 yrs old), though this subgroup included 3 trials, all of which used cranberry juice, one recruited females with no history of r-UTI, and spanned all three outcome definitions. Finally, their analysis did not address the specific question of formulation, having no sub-group analysis for juice versus tablet/capsule. Hence, so far, the specific question of whether tablet/capsule formulations of cranberry extract can reduce risk of r-UTI when defined using the gold-standard definition, remains unclear despite existing meta-analyses. We demonstrate, for the first time, that cranberry extract in tablet/capsule form is a feasible and effective therapeutic option for those at risk of r-UTI. To our way of thinking, studies using juice as treatment have no more than hypothesis generating and

academic value, given the aforementioned barriers to widespread long-term use. In terms of using cranberry extract in tablet/capsule form, there remains a need for large and high-quality RCTs. Moreover, our findings should hopefully help aid patient selection for future investigations, since low-risk patients or catheterized patients could potentially distort findings. Additionally, future studies should use the "gold-standard" definition of UTI, i. e. culture-confirmed UTI in symptomatic patients. Finally, commercially available cranberry extract preparations likely have variable PAC content and bioavailability, making it difficult to make general recommendations based on our results. Hence, future investigations should ideally report PAC bioavailability of the investigated formulation, preferably with measurement of plasma kinetics in at least a subset of included subjects.

Conflicts of Interest

The authors report no conflicts of interest.

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