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Moro, Christian; Phelps, Charlotte; Veer, Vineesha; Jones, Mark; Glasziou, Paul; Clark, Justin; Tikkinen, Kari A O; Scott, Anna Mae

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Review – Infections

Cranberry Juice, Cranberry Tablets, or Liquid Therapies for Urinary Tract Infection: A Systematic Review and Network Meta-analysis

Christian Moro [a,*], *Charlotte Phelps* [a], *Vineesha Veer* [a], *Mark Jones* [b], *Paul Glasziou* [b], *Justin Clark* [b], *Kari A.O. Tikkinen* [c,d,e], *Anna Mae Scott* [b,f]

[a] *Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Queensland, Australia;* [b] *Institute for Evidence-Based Healthcare, Bond University, Gold Coast, Queensland, Australia;* [c] *Department of Urology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland;* [d] *Department of Surgery, South Karelian Central Hospital, Lappeenranta, Finland;* [e] *Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada;* [f] *Nuffield Department of Population Health, University of Oxford, Oxford, UK*

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Abstract

Background and objective: With over 50% of women suffering from at least one episode of urinary tract infection (UTI) throughout their lifetime and an increasing prevalence of antimicrobial resistance, efforts need to be made to clearly identify the evidence supporting potential non-drug interventions. This study aims to compare the effects of cranberry juice, cranberry tablets, and increased liquids for the management of UTIs.

Methods: PubMed, Embase, and Cochrane CENTRAL were searched for randomised controlled trials. The primary outcome was the number of UTIs, and the secondary outcomes were UTI symptoms and antimicrobial consumption. A risk of bias assessment was performed using the Cochrane risk of bias tool, and the certainty of evidence was assessed using Grading of Recommendations Assessment, Development and Evaluation.

Key findings and limitations: A total of 20 trials (3091 participants) were included, with 18 studies highlighting a 54% lower rate of UTIs with cranberry juice consumption than no treatment and a 27% lower rate than placebo liquid. Cranberry juice also resulted in a 49% lower rate of antibiotic use than placebo liquid and a 59% lower rate than no treatment, based on a network meta-analysis of six studies. The use of cranberry compounds also reduced the prevalence of symptoms associated with UTIs.

Conclusions and clinical implications: With moderate to low certainty, the evidence supports the use of cranberry juice for the prevention of UTIs. While increased liquids reduce the rate of UTIs compared with no treatment, cranberry in liquid form provides even better clinical outcomes in terms of reduction in UTIs and antibiotic use and should be considered for the management of UTIs.

Patient summary: With the increasing prevalence of antimicrobial-resistant UTIs, alternate non-drug treatment options for its management are required. Available evidence supports the use of cranberry compounds and increases in fluid intake for managing UTIs.

* Corresponding author. Faculty of Health Sciences and Medicine, Bond University, Gold Coast, QLD 4226, Australia. Tel. +61 7 5595 4775.
E-mail address: cmoro@bond.edu.au (C. Moro).

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1. Introduction

Urinary tract infections (UTIs) are one of the most common bacterial infections. Over 50% of females [1,2] and 20% of males [3] suffer from at least one episode throughout their lifetime, and in children this is the most common bacterial infection [4]. Although antimicrobials have traditionally obtained a high immediate cure rate [5], there is an increasing prevalence of antibiotic resistance in the bacteria that cause UTIs. Some assessments have reported that over 90% of UTIs exhibited bacteria that was drug resistant, with most resistant to two or more antibiotics [6,7].

With microbial resistance starting to inhibit the effectiveness of antibiotics in the treatment of UTIs [8], now is the time to act and identify evidence-based non-drug interventions for the prevention and treatment of UTIs. The practice of reducing antibiotics also assists with the financial and clinical burden of their prescriptions, where UTIs are responsible for a significant percentage of clinical visits [9].

Increasing patient intake of liquids, or introducing cranberry juice or cranberry tablets, has been proposed as having potential benefits. However, the literature supporting this has been varied, and studies demonstrating the beneficial effects of cranberry [10,11] appear to arise as often as those that do not [12,13]. This is further confounded by having no studies that determine separately whether any therapeutic benefits observed in cranberry are due to the associated increase of liquids [14] or specific compounds within cranberry itself. These conditions and considerations present challenges for clinicians wishing to use literature to guide recommendations on treatment options for UTIs. For instance, the European Association of Urology guidelines consider current scientific evidence regarding the efficacy of cranberry products in the prevention of UTIs as inconclusive [53]. Based on the literature, is recommending liquids and/or cranberry compounds effective in the prevention, management, and treatment of UTIs? To answer this multivariable question, our study utilised the novel technique of a network meta-analysis, which enables a comparison between three or more interventions simultaneously across a network of studies [16,17].

2. Methods

This systematic review and network meta-analysis is reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) for Network Meta-analyses (NMA) extension checklist (see Supplementary Table 1) [18]. The review protocol was developed prospectively and registered on the Open Science Framework (https://osf.io/8x9m6).

2.1. Inclusion and exclusion criteria

2.1.1. Participants

We included studies of individuals of any age and gender who were at risk for UTIs, as defined by the study authors themselves (eg, specified number of UTIs in 12 mo). We excluded studies of catheterised participants unless the study included both catheterised and non-catheterised participants, and the results for the latter were reported separately.

2.1.2. Intervention and comparators

We included all studies that compared at least two of the following interventions:

1. Cranberry non-liquid products: for example, tablet, capsule, and fruit.
2. Cranberry liquid: for example, juice, cocktail, and concentrate (including mixed-flavour juices that include cranberry juice as a primary ingredient).
3. Liquid other than cranberry: for example, water, non–cranberry juice (eg, apple, pineapple, or tomato), beer, and D-mannose dissolved in 250 ml of liquid.
4. Comparisons with no treatment (in a deviation from the protocol) to further clarify the differential impact of the intake of cranberry in the liquid form versus that in the non-liquid (physical) form.

2.1.3. Outcomes

The primary outcome was the number of UTIs in each group, as defined by the study authors. The secondary outcomes included UTI symptoms (eg, increased bladder sensation, dysuria, urgency, frequency, and/or pain in the lower urinary tract) [19] and antimicrobial consumption.

2.1.4. Study design

We included randomised controlled trials (RCTs) of any design, pseudorandomised trials, and non-randomised controlled clinical trials. All other primary study designs were excluded. Where evidence syntheses (eg, systematic reviews and scoping reviews) were identified, we examined their lists of included studies to check for additional studies.

2.2. Search strategies to identify studies

2.2.1. Database searches

We searched PubMed, Embase, and Cochrane CENTRAL from inception until September 25, 2023. The search string was designed in PubMed and translated for use in other databases using the Polyglot Search Translator [20]. Complete search strings for all databases are provided in the Supplementary material. A forward and backward citation analysis was conducted on September 29, 2023, using SpiderCite (https://sr-accelerator.com/#/spidercite). No restrictions by language or publication date were imposed. We included publications that were published in full. Publications that were available only as abstracts were included if these had a corresponding clinical trial registry record or other public report, with the additional information required for inclusion.

2.3. Study selection and screening

Two authors independently screened the titles and abstracts against the inclusion criteria. One review author retrieved the full text, and two authors screened the full text for inclusion. Any disagreements were resolved by discussion or reference to a third author. The selection process was recorded in sufficient detail to complete a PRISMA flow diagram (Fig. 1), and a list of excluded studies with reasons for exclusions was generated (Supplementary Table 2). Two review authors independently assessed the risk of bias for each included study using the Risk of Bias Tool 1, as outlined in the *Cochrane Handbook* [21]. There was no need to

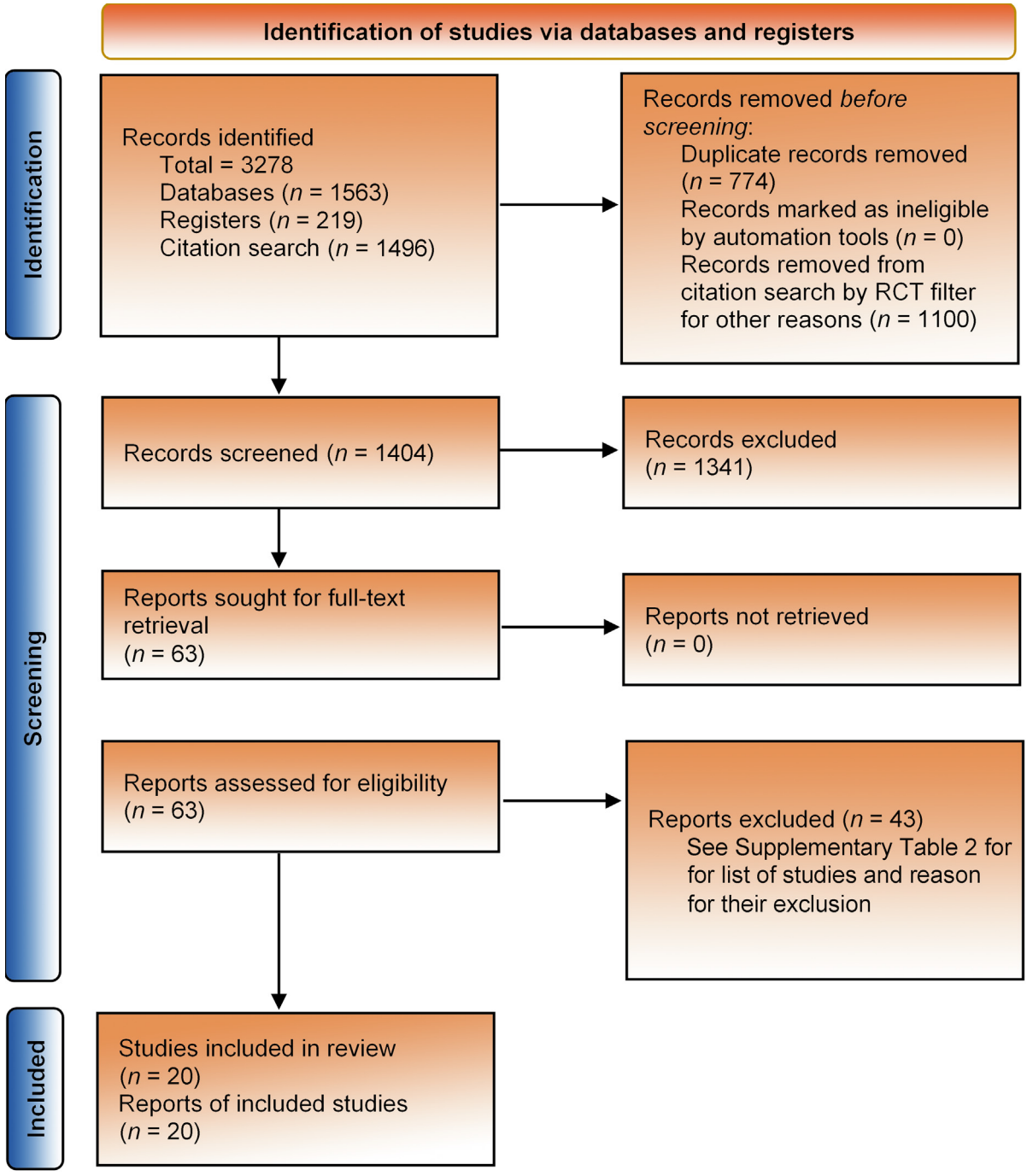

Fig. 1 – PRISMA flow diagram [45]. Supplementary Table 2 contains the references and reasons for full-text excluded articles and on-going clinical trials that do not have results available. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT = randomised controlled trial.

contact the investigators or study sponsors to provide the missing data.

2.4. *Measurement of effect*

We used risk ratios or rate ratios for dichotomous outcomes, risk ratios for results reporting the number of individuals with an event, and rate ratios for the results reporting the number of events only. For continuous outcomes (eg, severity of symptoms), we used mean difference or standardised mean difference as appropriate.

A network meta-analysis was performed based on the contrast-based frequentist random-effect method [22]. A Poisson model was specified with a log link and log of the number of participants in each treatment group as the offset. Estimates are reported as rate ratios and 95% confidence intervals. The goodness of fit of the model was assessed using the ratio of generalised chi-square to degrees of freedom (values >1 indicate overdispersion). We used the I^2 statistics to measure heterogeneity among the included trials.

2.5. Assessment of reporting biases

For the 14 RCTs included, we prepared a funnel plot to examine the possibility of occurrence of small study effects.

2.6. Data synthesis (standard pair-wise meta-analysis)

We undertook meta-analyses only when meaningful (when two or more studies or comparisons reported the same outcome); anticipating heterogeneity, we used a random-effect model. RevMan 5 (Cochrane Collaboration, London, UK) was used to calculate the treatment effect for meta-analyses where applicable.

2.7. Subgroup and sensitivity analyses

Where data were sufficient, we had intended to conduct the subgroup analyses by: (1) gender, (2) severity condition/diagnosis, (3) type of intervention and comparator, and (4) timing of outcome. Sixteen of the 20 included studies comprised a large majority of female participants, precluding the subgroup analysis by gender. The number of included studies for five of the six direct comparisons (all except the comparison of cranberry liquid with non–cranberry liquid) ranged from one to four studies. We therefore elected not to conduct prespecified subgroup analyses by severity or by timing of the outcome for any of the comparisons. Data were sufficient to conduct analyses by type of intervention and comparator for the primary (number of UTIs) and secondary (antibiotic consumption), but not the secondary outcome—UTI symptoms.

We prespecified that we would conduct a sensitivity analysis by including versus excluding studies at a high risk of bias. The two included studies were controlled clinical trials [23,24]. This impacts the analysis of the primary outcome (cranberry liquid vs no treatment comparison) and the secondary outcome (UTI symptoms). The impact of excluding these studies is indicated in the relevant results section.

2.8. Network geometry and meta-analysis (NMA)

The statistical analysis consisted of the following steps:

1. First, the network geometry was drawn to graphically represent the network relationships. Treatments were grouped into four categories: (1) cranberry products (non-liquid), (2) cranberry juice, (3) other liquids, and (4) no treatment.
2. Second, consistency and transitivity were assessed. Consistency was assessed by examining whether the outcomes of direct and indirect comparisons are consistent. Transitivity was assessed by exploring whether effect modifiers (see the subgroup analysis) are balanced across any treatment groups compared indirectly.
3. Third, a network meta-analysis was performed using SAS OnDemand for Academics based on the contrast-based frequentist random-effect method illustrated by Rott et al [22]. A Poisson model was specified with a log link and log of the number of participants in each treatment group as the offset. Estimates are reported as rate ratios and 95% confidence intervals. The goodness of fit of the model was assessed using the ratio of generalised chi-square to degrees of freedom (values >1 indicate overdispersion). Results from a pairwise meta-analysis for the primary outcome are reported for informal comparison with the network meta-analysis results.

2.9. Overall certainty of the body of evidence (GRADE)

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of the body of evidence for the primary outcome. Two reviewers independently applied the GRADE criteria and reached consensus judgements through discussion. Certainty for each outcome was rated as very low (the true effect is probably markedly different from the estimated effect), low (the true effect might be markedly different from the estimated effect), moderate (true effect is probably close to the estimated effect), or high (the authors have a lot of confidence that the true effect is similar to the estimated effect) [25].

Certainty of the evidence for each outcome was determined by considering eight GRADE factors, five of which may lead to rating down certainty (risk of bias, indirectness, inconsistency, imprecision, and publication bias) and three may result in rating up certainty (large effect, dose response, and all plausible confounders and biases). Reasons for downgrading the evidence were classified as "serious" (downgrading the certainty rating by one level) or "very serious" (downgrading the certainty by two levels); when the reason is not serious enough to warrant downgrading, it was classified as "no limitation". Certainty of the evidence was rated up one level when a large magnitude of effect exists, when there was a dose-response gradient, and when all plausible confounders or other biases would reduce a demonstrated effect or suggest a spurious effect when no effect was observed, as per the guidance outlined in GRADE guideline 9 [26]. The baseline certainty rating for all but two included studies [23,24] was high. Supplementary Table 3 provides the full breakdown of the GRADE assessment.

3. Results

3.1. Results of the search

Searches of electronic databases, clinical trial registers, and a forward and backward (citation) search yielded 3278 references. After deduplication, 1404 references were screened in titles and abstracts, and 1341 references were excluded. A total of 63 references were screened in full text, and of those, 43 were excluded (see Supplementary Table 2 for reasons of study exclusion). Twenty studies met the inclusion criteria.

3.2. Included studies

Twenty trials (18 RCTs and two non-RCTs) were included in this review, with a collective population of 3091 participants (Table 1). The population of participants included 2745 (88.8%) females and 346 (11.1%) males. The duration of follow-up ranged from 2 to 12 mo. The mean or median study age of the study participants ranged from 4 to 87 yr of age. There was variation in the study criteria for previous

Table 1 – Description and characteristics of the studies included in the review

Author (year) Location	Study design Follow-up	No. of participants (*N* each arm)	Gender	Age (yr)	Previous UTIs/definition of UTI	Cranberry intervention Dose, frequency, duration	Comparator(s) Dose, frequency, duration	Primary outcome
Avorn (1994) [27] USA	RCT 6 mo	153 (81 control, 72 cranberry)	100% female, 0% male	Mean 78.5	>1 UTIs in the past 12 mo And bacteriuria (organisms numbering $>10^5$/ml, regardless of organism) with pyuria	A1: cranberry juice 300 ml, 1× daily, 6 mo	A2: placebo liquid, 1× daily, 6 mo	Quantitative test for bacteriuria and presence for white blood cells
Barbosa-Cesnik (2011) [34] USA	RCT 6 mo	319 (164 control, 155 cranberry)	100% female, 0% male	Mean 21	>3 urinary symptoms in the past 12 mo And positive urine culture, defined as ≥1000 cfu/ml urine of a known uropathogen	A1: cranberry juice 27%, 240 m, 2× daily, 6 mo	A2: placebo liquid, 240 ml, 2× daily, 6 mo	Risk of UTI recurrence during study period
Cowan (2012) [35] Scotland	RCT 6 wk	128 (64 control, 64 cranberry)	46.9% female, 53.1% male	Median 67.5 Range 27–89	Previous number of UTIs not reported Assessments based on bacterial positive urine sample ($>10^5$ per ml or heavy growth) and/or other abnormal findings	A1: cranberry juice, 16 000 ml, 2× daily, 2 wk	A1: placebo liquid, 16 000 ml, 2× daily, 2 wk	Risk of urinary symptoms or UTI occurrence
De Leo (2017) [36] Italy	RCT 3 mo	150 (50 control, 100 cranberry)	100% female, 0% male	Range 40–50	No. of episodes prior to study (8.7 ± 0.8 control, 8.5 ± 1, cranberry l) Assessments based on positive urine culture in past 6 mo	A1: cranberry juice, 250 ml, 1× daily, during first 10 d of each month, 3 mo	A2: no intervention	Occurrence of urinary symptoms and/or UTI
Ferrara (2009) [30] Italy	RCT 6 mo	84 (29 placebo, 28 cranberry, 27 *Lactobacillus*)	100% female, 0% male	Mean 7.5 Range 3–14	≥1 UTIs in the past 12 mo UTI symptoms (such as frequency, urgency, dysuria, haematuria, nocturia, fever, or back or hip pain)	A1: cranberry juice 50 ml concentrate in 200 ml, 1× daily, 6 mo	A2: *Lactobacillus* GG juice 4×10^7 cfu of *Lactobacillus* GG in 100 ml, 1× for 5 d a month, 6 mo A3: not reported	Occurrence of UTI during study period
Juthani-Mehta (2010) [46] USA	RCT 6 mo	56 (17 control, 20 cranberry 1× daily, 19 2× daily)	82.1% female, 17.9% male	Mean 87	Elderly residents of nursing homes, who had dementia and were at risk of UTIs	A1: cranberry tablet, 16.25 mg, 1× daily, 6 mo A2: cranberry tablet, 2× daily, 16.25 mg, 1× daily, 6 mo	A3: no intervention throughout the study	Occurrence of UTI during study period
Kontiokari (2001) [31] Finland	RCT 12 mo	150 (50 control, 50 cranberry, 50 lactobacillus)	100% female, 0% male	Mean 30	Previous UTIs not reported Assessments based on bacterial positive urine sample for *Escherichia coli* (10^5 cfu/ml) with no antimicrobial prophylaxis	A1: cranberry-lingonberry juice 7.5 g cranberry and 1.7 g lingonberry concentrate in 50 ml, 1× daily, 6 mo	A2: *Lactobacillus* GG juice 4×10^7 cfu of *Lactobacillus* GG in 100 ml, 1× for 5 d a month, 12 mo A3: not reported	Occurrence of symptomatic UTI, defined as bacterial growth $>10^5$ cfu/ml
Ledda (2015) [24] Italy	CCT 2 mo	44 (22 control, 22 cranberry)	75% female, 25% male	Mean 39	>2 UTIs in the past 6 mo or >3 UTIs in the past 12 mo	A1: cranberry tablet, 25–35% PAC, 1× daily, 60 d, with standard management	A2: standard management	Occurrence of UTI during study period
Ledda (2017) [23] Italy	CCT 2 mo	36 (17 control, 19 cranberry)	53% female, 47% male	Range 12–18	>2 UTIs in the past 6 mo or >3 UTIs in the past 12 mo	A1: cranberry tablet, 36 mg PAC, 1× daily, 60 d, with standard management	A2: standard management	Occurrence of UTI episodes
Maki (2016) [28] USA /France	RCT 6 mo	373 (188 control, 185 cranberry)	100% female, 0% male	Mean 40.9	>2 UTIs in the past 12 mo	A1: cranberry juice 27%, 240 ml, 1× daily, 6 mo	A2: placebo liquid, 240 ml, 1× daily, 6 mo	Clinical UTI incidence density (occurrence of UTI divided by observation time).
McMurdo (2005) [32] Scotland	RCT 35 d	376 (187 control, 189 cranberry)	68% female, 32% male	Mean 81.4	Previous UTIs not reported Assessments based on bacterial positive urine sample (10^4 cfu/ml)	A1: cranberry juice 25% PAC, 150 ml, 2× daily, 35 d	A1: placebo liquid, 150 ml, 2× daily, 35 d	Time to onset of first UTI

(continued on next page)

Table 1 (*continued*)

Author (year) Location	Study design Follow-up	No. of participants (*N* each arm)	Gender	Age (yr)	Previous UTIs/definition of UTI	Cranberry intervention Dose, frequency, duration	Comparator(s) Dose, frequency, duration	Primary outcome
Murina (2021) [47] Italy	RCT 5 mo	55 (17 control, 19 cranberry 1× daily, 19 cranberry 10 d/mo)	100% female, 0% male	Mean 39.3 Range 20–46	>2 UTIs in the past 6 mo or >3 UTIs in the past 12 mo Assessments based on the presence of ≥103 cfu/ml	A1: cranberry juice, 36 mg PAC, 180 ml, 1× for 10 d/mo, 90 d A2: cranberry juice, 36 mg PAC, 180 ml, 1× daily, 90 d	A3: no intervention throughout the study	Reoccurrence of UTI during study period
Salo (2012) [29] Finland	RCT 12 mo	255 (134 control, 129 cranberry)	91% female, 9% male	Mean 4 Range 1–16	≥1 UTI in the past 2 mo Assessments based on UTI symptoms and growth of single bacteria strain (10^5 cfu/ml)	A1: cranberry juice 41 g cranberry per 1000 ml, up to 300 ml, 1× or 2× daily, 6 mo	A2: placebo liquid per 1000 ml, up to 300 ml, 1× or 2× daily, 6 mo	Reoccurrence of UTI during study period
Sengupta (2011) [33] India	RCT 3 mo	60 (16 control, 21 500 mg cranberry, 23 1000 mg cranberry)	100% female, 0% male	Range 18–40	History of painful urination, frequency, blood in the urine, or pain in the suprapubic area	A1: cranberry tablet, 250 mg per tablet, 2× daily, 90 d A2: cranberry tablets, 500 mg per tablet, 2× daily, 90 d	A3: no intervention throughout the study	Occurrence of UTI during study period
Stapleton (2012) [48] USA	RCT 6 mo	186 (31 4 oz control, 30 8 oz control, 63 4 oz cranberry, 62 8 oz cranberry)	100% female, 0% male	Mean 25 Range 18–45	≥1 clinician diagnosed UTIs in the past 12 mo and positive urine culture, defined as $>10^3$ cfu/ml of uropathogen	A1: cranberry juice 27%, 4 oz, 1× daily, 6 mo A2: cranberry juice 27%, 4 oz, 1× daily, 6 mo	A3: placebo liquid, 8 oz, 1× daily, 6 mo A4: placebo liquid, 4 oz, 1× daily, 6 mo	Time to UTI (symptoms plus pyuria)
Stothers (2002) [49] Canada	RCT 12 mo	150 (50 control, 50 cranberry juice, 50 cranberry tablet)	100% female, 0% male	Mean 42.3 Range 21–72	>2 UTIs in the past 12 mo Assessments based on symptomatic, single-organism, culture-positive sample	A1: cranberry juice, 250 ml, 3× daily, 12 mo A2: cranberry tablet, 2× daily, 12 mo	A3: placebo liquid, 250 ml, 3× daily and placebo tablets, 2× daily, 12 mo of each product	Occurrence of symptomatic UTI
Takahashi (2013) [50] Japan	RCT 2 mo	213 (106 control, 107 cranberry)	100% female, 0% male	Range 20–79	Clinically diagnosed with multiple UTI relapses and received antibiotic agents	A1: cranberry juice 40 mg PAC per 125 ml, 1× daily, 24 wk	A2: placebo liquid, 125 ml, 1× daily, 24 wk	Frequency of bacteriuria
Temiz (2018) [44] Turkey	RCT 3 mo	60 (20 control, 20 cranberry, 20 education)	31.7% female, 68.3% male	Mean 63.83	68.3% of the patients had a history of UTI Urine culture was positive if $\geq 10^5$ cfu/ml or more bacteria with no more than two species of organisms was present	A1: cranberry tablets, 18% PAC (9 mg), 2× daily, 3 mo	A2: verbal info about UTIs and informational brochure, once at the start of the study A3: no intervention throughout the study	Occurrence of UTI during study period
Wan (2016) [51] Taiwan	RCT 12 mo	55 (27 control, 28 cranberry)	0% female, 100% male	Mean 9.5	≥3 UTIs per year or ≥2 UTIs per half year Culture positive, defined as bacteria count ≥1 × 105	A1: cranberry juice, 120 ml, 1× daily, 6 mo	A2: placebo liquid, 120 ml, 1× daily, 6 mo	Time to UTI (symptoms plus pyuria)
Wing (2008) [52] USA	RCT 5 mo	188 (63 control, 67 cranberry 1× daily, 58 cranberry 3× daily)	100% female, 0% male	Mean 26.4	Previous UTI was not reported. Urine culture with $\geq 10^5$ of a single uropathogen	A1: cranberry juice 27%, 240 ml, 3× daily, intent-to-treat duration with median being 152.5 d A2: cranberry juice 27%, 240 ml, 1× daily and placebo liquid, 240 ml, 2× daily, intent-to-treat duration with median being 177 d of each product	A3: placebo liquid, 240 ml, 3× daily, intent-to-treat duration with median being 171 d	Episodes of bacteriuria

CCT = controlled clinical trial; RCT = randomised controlled trial; UTI = urinary tract infection.

UTIs, with most studies reporting more than one UTI in the previous 12 mo to up to three or more UTIs in the previous 12 mo. Fifteen of the included studies (75%) evaluated cranberry in liquid form (eg, juice) and five studies (25%) evaluated cranberry in its physical form (eg, tablet or supplement). The duration of intake was evaluated most frequently for 6 mo but ranged from 2 wk to 12 mo. Thirteen studies (65%) evaluated placebo liquid as the comparator, four (20%) had no intervention, and three studies (15%) had standard management (ie, lifestyle advice and/or hygiene advice).

While most studies performed were specific to adult females (12/20), one was in adult males with the remainder assessing both genders. Four studies were performed in children. As there are different management requirements for paediatric patients, it was unclear whether the UTI presentations in children should be excluded. To assess this as a subgroup analysis, we compared the treatment effects for adults and children using a likelihood ratio test. We did this by adding interaction terms (age group × treatment effect) to the network meta-analysis model and testing whether these resulted in a better fitting model. The findings showed no evidence of interaction using a likelihood ratio test ($p = 0.21$); hence, we conclude that there is insufficient evidence that the treatment effects are different for adults and children.

Although the exact classification of a UTI differs between studies, in each case, these were confirmed to comply with the European Association of Urology definition for a symptomatic uncomplicated UTI: an acute, sporadic, or recurrent lower and/or upper UTI, limited to non-pregnant women with no known relevant anatomical and functional abnormalities within the urinary tract or comorbidities.

3.3. Risk of bias

Studies were generally at a low or an unclear risk of bias. Two out of 20 studies were rated at a high risk of bias for random sequence generation because these were non-randomised controlled clinical trials. Nine studies were at a high risk of bias due to the lack of blinding of participants and personnel. Five studies were rated to have a high risk of bias for other biases, due to potential biases from funding and conflict of interest considerations. Three studies were funded by Ocean Spray Cranberries Inc (Lakeville-Middleboro, Massachusetts) [27–29]; two studies used cranberry interventions provided by pharmaceutical companies (Fig. 2 and Supplementary Fig. 1) [23,24].

3.4. Primary outcome: urinary infection rate

There were 18 studies that contributed to the analysis, with 14 direct comparisons between cranberry juice and placebo liquid, four direct comparisons between cranberry juice and no treatment, one direct comparison between cranberry juice and cranberry tablet, three direct comparisons between cranberry tablet and no treatment, one direct comparison between cranberry tablet and placebo liquid, and three direct comparisons between no treatment and placebo liquid (see Supplementary Fig. 2).

The results in Table 2 provide evidence that the cranberry juice group had a lower rate of UTI by 27% than the placebo liquid group (moderate certainty evidence; see Supplementary Table 3 for GRADE) and a lower rate of UTIs by 54% than the no treatment group (very low certainty evidence), and no treatment had an increased rate of UTI by 58% compared with placebo liquid. A sensitivity analysis, which excluded one study at a high risk of bias from the cranberry juice to no treatment comparison, changed the rate of UTIs from a decrease by 54% to a decrease by 49%. No treatment had an increased rate of UTIs by 58% compared with placebo liquid (low certainty evidence). There is insufficient evidence of a difference in rates of UTIs between cranberry tablet and each of the other three comparators, all of which had low (cranberry tablet vs no treatment) or very low certainty (cranberry tablet vs placebo liquid and cranberry tablet vs cranberry liquid) evidence. The ratio of generalised chi-square to degrees of freedom was 0.90, indicating a good fit.

To check for consistency in studies included within the network meta-analysis, a pairwise meta-analysis was performed (Table 3). The result for cranberry juice was identified to be very similar to that of the network meta-analysis. This is because there were 14 direct comparisons between cranberry juice and placebo liquid; hence, the indirect comparisons added minimal additional information. By con-

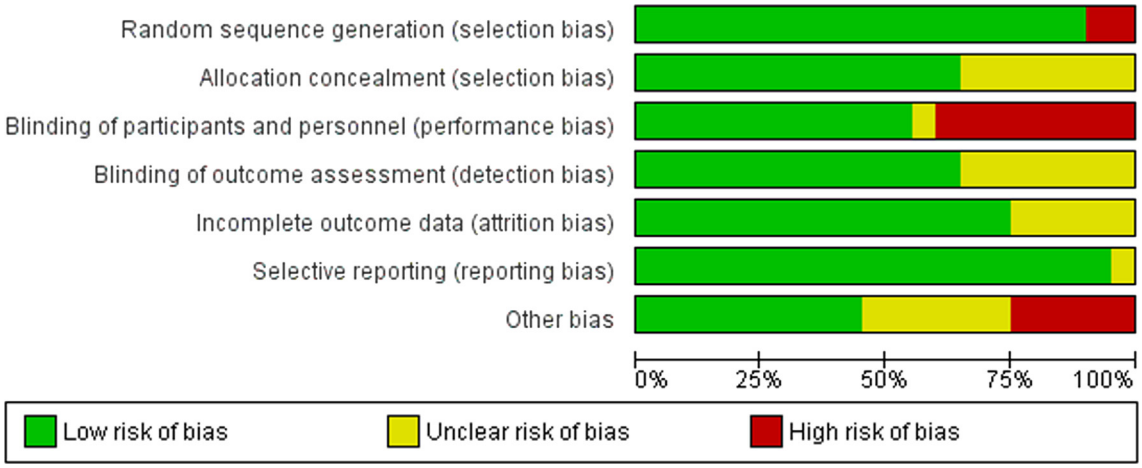

Fig. 2 – Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Table 2 – Results from the network meta-analysis

Treatment group	Comparator group	Rate ratio	95% CI	*p* value
Cranberry juice	Placebo liquid	0.73	0.59–0.91	0.005
Cranberry tablet	Placebo liquid	1.04	0.62–1.73	0.89
No treatment	Placebo liquid	1.58	1.07–2.35	0.022
Cranberry juice	No treatment	0.46	0.31–0.68	<0.0001
Cranberry tablet	No treatment	0.65	0.42–1.03	0.068
Cranberry juice	Cranberry tablet	0.70	0.42–1.17	0.18

CI = confidence interval.

Table 3 – Results from the pairwise meta-analysis of urinary infection rate

Treatment group	Comparator group	Type of studies (total participants)	Rate ratio	95% CI	*p* value
Cranberry juice	Placebo liquid	14 RCTs (2400 participants)	0.74	0.60–0.91	0.004
Cranberry tablet	Placebo liquid	1 RCT (100 participants)	0.56	0.25–1.22	0.16
No treatment	Placebo liquid	3 RCTs (189 participants)	1.44	0.83–2.48	0.19
Cranberry juice	No treatment	3 RCTs + 1 CCT (234 participants)	0.31	0.18–0.54	<0.0001
Cranberry tablet	No treatment	1 RCT (100 participants)	0.70	0.32–1.51	0.36
Cranberry juice	Cranberry tablet	3 RCTs (114 participants)	1.11	0.45–2.77	0.80

CCT = controlled clinical trial (non-randomised); CI = confidence interval; RCT = randomised controlled trial.

Table 4 – Results from the network meta-analysis of antibiotic use

Treatment group	Comparator group	Rate ratio	95% CI	*p* value
Cranberry juice	Placebo liquid	0.51	0.30–0.87	0.014
Cranberry tablet	Placebo liquid	0.47	0.07–3.17	0.44
No treatment	Placebo liquid	1.25	0.53–2.94	0.62
Cranberry juice	No treatment	0.41	0.17–1.02	0.055
Cranberry tablet	No treatment	0.38	0.07–2.08	0.26
Cranberry juice	Cranberry tablet	1.08	0.16–7.44	0.94

CI = confidence interval.

trast, the results for the other comparisons are somewhat different for the pairwise meta-analysis from those for the network meta-analysis due to the limited number of direct comparisons. However, the results between the network meta-analysis and pairwise meta-analysis are all consistent in terms of the confidence interval overlapping.

3.5. *Secondary outcome: antibiotic use*

Although there were only limited studies assessing the impact of antibiotic use, an attempt was made to investigate any relationships between treatments and comparators. Six studies contributed to the analysis, with five direct comparisons between cranberry juice and placebo liquid, two direct comparisons between cranberry juice and no treatment, no direct comparison between cranberry juice and cranberry tablet, one direct comparison between cranberry tablet and no treatment, no direct comparison between cranberry tablet and placebo liquid, and two direct comparisons between no treatment and placebo liquid [27,29–33]. Only antibiotic use within the timeframe of the study was included.

The results in Table 4 provide some evidence that the cranberry juice group had a lower rate of antibiotic use by 49% than the placebo liquid group and a lower rate of antibiotic use by 59% than the no treatment group, but insufficient evidence of a difference for all other comparisons. The ratio of generalised chi-square to degrees of freedom was 0.23, indicating a good fit.

3.6. *Secondary outcome: symptoms*

Seven studies reported on urinary symptoms. Three studies [23,24,33] were meta-analysable. Two studies [23,24] compared physical cranberry tablet and lifestyle advice with lifestyle advice alone. One study [33] compared physical cranberry tablet low dose (500 mg/d) with physical cranberry tablet high dose (1000 mg/d) and no treatment. For reporting of UTI symptoms, the physical cranberry groups were combined and compared with the no treatment group.

All three studies (140 patients) reported the numbers of people who were UTI symptom free (ie, did not experience UTI symptoms). The difference between the cranberry and comparator groups was significant, favouring cranberry (risk ratio 5.22, 95% confidence interval 1.26–21.55, $p = 0.02$); heterogeneity among the included studies was low ($I^2 = 36\%$; Fig. 3). A sensitivity analysis (excluding studies with three or more domains rated at a high risk of bias) would have precluded the meta-analyses, as two of the three studies contributing data [23,24] would have been excluded.

Four studies were not meta-analysable. Of these four studies, three reported combined UTI symptoms [29,34,35], and all three compared cranberry juice with pla-

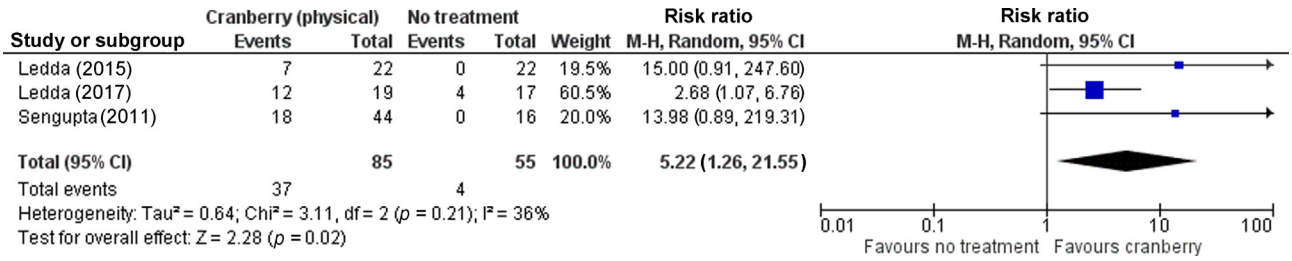

Fig. 3 – Cranberry tablet versus comparator: the number of people who were free of UTI symptoms. CI = confidence interval; M-H = Mantel–Haenszel; UTI = urinary tract infection.

cebo liquid. One study reported that there were "overall no marked differences" between the cranberry juice and placebo liquid groups, in terms of urinary and vaginal symptoms at 3 d, 1–2 wk, and >1 mo [34]. Another study reported no statistical difference (p = 0.267) between the cranberry juice and placebo liquid groups, in terms of grade 3 urinary symptoms [35]. One study [28] found similar numbers of the fractions of clinical UTI diagnoses for which the participants reported two or more UTI symptoms (38/39 diagnoses in the cranberry group and 66/67 in the placebo liquid group) and the fractions of clinical UTI diagnoses for which the participants reported three or more UTI symptoms (38/39 diagnoses in the cranberry group and 61/67 in the placebo liquid group).

One study [36] compared cranberry juice with no treatment, and separately reported the mean number of episodes in each group, for dysuria, painful urination, and frequent urination. After 3 mo, the mean (±standard deviation) number of episodes of dysuria was significantly lower in the cranberry group (2.0 ± 0.5) than in the no treatment group (6 ± 0.3); the mean number of episodes of painful urination was also significantly lower (cranberry mean 2.1 ± 0.5; no treatment mean 7 ± 2), as were the episodes of painful urination (cranberry mean 1.8 ± 0.2; no treatment mean 6.2 ± 1.8).

4. Discussion

4.1. Summary

The network meta-analysis identified moderate to very low certainty evidence that cranberry juice results in a 54% lowered rate of UTIs compared with no treatment (very low certainty) and a 27% lowered rate compared with placebo liquid (moderate certainty). No treatment resulted in a 58% increased rate of UTIs than placebo liquid (low certainty) and a 35% increased rate compared with cranberry tablets (low certainty). Cranberry juice also resulted in a 49% lower rate of antibiotic use than placebo liquid and a 59% lower rate than no treatment. The use of cranberry compounds also reduced the prevalence of symptoms associated with UTIs. While increased liquids benefit the rate of UTIs and reduce antibiotic use, and cranberry compounds benefit symptoms of infection, the combination of these, in cranberry juice, provides clear and significant clinical outcomes for the reduction in UTIs and antibiotic use. The evidence supports the use of cranberry juice for the prevention and treatment of UTIs. However, the evidence sits at moderate to low certainty, highlighting the need for additional RCTs to be conducted.

4.2. Comparison with existing literature

It has been clear that the dual benefits of increased liquids alongside cranberry have confounded the literature for some time. Although many studies support the use of cranberry itself [11], when compared directly with increased liquids (or a placebo that involved liquids), there is the potential that only minimal changes are detected due to a relatively small effect size between the two interventions. In comparison, increasing liquids as well as cranberry presents a confounding effect and becomes quite important for patients. As such, the recommendation is to combine increased liquids with cranberry-based compounds. The active component within the cranberry is unknown but potentially related to its concentration of proanthocyanidins [37], which have been identified to inhibit some bacterial and fungal growths [37–39], or other bioactive compounds that are present in both cranberries and associated cranberry juices [40].

Alongside cranberry consumption, the recommendation to increase regular liquid consumption may provide longer-term benefits to UTI prevention by reducing dehydration. Dehydration is particularly prevalent in older people and likely presents a strong risk factor for bacterial infections [41]. The direct research into the links between dehydration and UTIs occasionally contradicts due to inconsistencies between exact amounts of liquid and the individual participant's history of UTIs [42,43]. However, it is likely that the fewer voids per day, the concentrated and acidic urine, and the inhibited immune function correlated with dehydration all contribute to the increased susceptibility to UTIs.

4.3. Strengths and limitations

Some planned findings, such as impacts on antibiotic use, were reduced due to limited studies. Some challenges were identified when collating data, as the criteria for reporting "recurrent UTIs" varied significantly. For example, some studies considered more than one UTI to be recurrent, while others required more than three UTIs over varied periods (ie, from <6 up to 12 mo). Some studies required positive bacteria culture to be confirmed before reporting it as a UTI.

An additional limitation was that some studies investigating the effectiveness of cranberry tablets provided education along with the cranberry intervention, which may have impacted the rates of recurrence. Temiz and Cavdar [44] provided educational content in the form of verbal information about UTIs and an informational brochure,

while Ledda et al [23,24] included educational content as lifestyle and hygiene advice.

Of the 20 studies included, most participants were females. Twelve studies assessed only females. Although seven studies included mixed genders, four of these had considerably (68–91%) more females than males, with only one study investigating solely males. As such, the limited number of studies and (male) participants meant that comparisons between genders were not possible.

5. Conclusions

The evidence supports the use of cranberry juice for the prevention of UTIs. While increased liquids benefit the rate of UTIs and reduce antibiotic use, and cranberry compounds benefit symptoms of infection, the combination of these, in cranberry juice, provides clear and significant clinical outcomes for the reduction in UTIs and antibiotic use, and should be considered for the management of UTIs.

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Study concept and design: Moro, Glasziou, Scott.
Acquisition of data: Moro, Phelps, Veer, Glasziou, Tikkinen, Clark, Jones, Scott.
Analysis and interpretation of data: Moro, Phelps, Veer, Glasziou, Tikkinen, Jones, Scott.
Drafting of the manuscript: Moro, Phelps, Veer, Glasziou, Jones, Clark, Scott.
Critical revision of the manuscript for important intellectual content: Moro, Scott, Glasziou, Tikkinen.
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Appendix A. Supplementary data

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