Author's Accepted Manuscript

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PII: S0022-5347(17)39295-9
DOI: 10.1016/j.juro.2017.03.078
Reference: JURO 14628

To appear in: *The Journal of Urology*
Accepted Date: 7 March 2017

Please cite this article as: Luís Â, Domingues F, Pereira L, Can cranberries contribute to reduce the incidence of urinary tract infections? - A systematic review with meta-analysis and trial sequential analysis of clinical trials, *The Journal of Urology*® (2017), doi: 10.1016/j.juro.2017.03.078.

Can cranberries contribute to reduce the incidence of urinary tract infections? - A systematic review with meta-analysis and trial sequential analysis of clinical trials

Running head: Cranberries and urinary tract infections

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Key words: urinary tract infections, cranberries, systematic review, meta-analysis, trial sequential analysis

ABSTRACT

Purpose: To clarify the association between cranberries intake and the prevention of urinary tract infections (UTIs).

Methods: It was performed a systematic review, complied with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) statement, followed by a meta-analysis and trial sequential analysis (TSA) of clinical trials.

Results: The results clearly show the potential use of cranberries in a clinical condition of UTI. The weighted risk ratio observed (WRR=0.6750; 95% CI:0.5516-0.7965; *p*-value<0.0001) indicates that the use of cranberry products significantly reduced the incidence of UTIs. The results of subgroup analysis demonstrate that the patients at some risk to develop UTIs were more susceptible to the effects of the ingestion of cranberries.

Conclusions: The results of the present work could be used by physicians to recommend the ingestion of cranberries to reduce the incidence of UTIs, particularly in individuals with recurrent UTIs, and so to also reduce the use of antibiotics which can lead to the worldwide emergence of antibiotic resistant microorganisms.

INTRODUCTION

Urinary tract infections (UTIs) are common and are among the most frequent medical conditions requiring outpatient treatment.[1] Approximately 80% of all UTIs occur in women, and 20% to 30% of women with a UTI will have a recurrence.[1] Recurrent UTIs (rUTIs), defined as at least three episodes of UTI in the last 12-months or two episodes in the last 6-months, can occur in susceptible individuals and are a significant source of patient morbidity and health care costs.[2] In individuals with rUTIs, low dose antibiotic prophylaxis for several months can be recommended.[1] However, antibiotics are the main cause for the development of antibiotic resistance and such prolonged treatments can lead to increased resistance.[1] The increasing prevalence of *Escherichia coli* isolates resistant to anti-microbial agents has stimulated interest in non-antibiotic methods for the prevention of UTIs.[1] Prophylaxis with cranberries is a potential prevention strategy with the health benefits being associated with the high concentrations of polyphenols such as proanthocyanidins (PACs) found in these berries.[3,4] PACs are stable phenolics with anti-adhesion activity against *E. coli*,[3] acting as receptor analogs and inhibiting the adhesion of *E. coli* to cells by binding to the fimbrial tips.[3]

The effects of the cranberries ingestion in the prevention of UTIs were systematized in two previous reviews with meta-analysis.[5,6] The most recent suggested that there is no sufficient evidence that cranberries decrease the number of UTIs, since the pooled findings are based on a small number of studies.[5] Taking this into account, together with the results of recent clinical trials evaluating cranberries for the prevention of UTIs, this systematic review was performed, complying with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) statement, followed by a meta-analysis and trial sequential analysis (TSA), a newer approach which can assist in reducing the likelihood of a type I error, to clarify the association between cranberries intake and the prevention of UTIs.

METHODS

Search strategy

The search was conducted (September 2016) in several electronic databases (Pubmed, Scopus, SciELO, Cochrane Library, Web of Science) using the terms (cranberr* OR *Vaccinium*) AND (urinary tract infections OR UTI) AND clinical trial AND human.

Following the PRISMA statement, titles and abstracts of records retrieved were screened and the full texts of those considered relevant were analyzed. Two authors independently performed the literature search, with disagreements resolved by consensus with a third author. To be included in this work, studies must to be clinical trials in humans; present a true control group; and report the number of patients experiencing at least one UTI at the end of the follow-up period (outcome of interest).

Data extraction

Two authors independently assessed and extracted the data. Information was collected on characteristics of studies (Table 1) and on the proportion of patients with at least one UTI. Risk Ratio (RR) was used as the measure of effect for the outcome of interest.

Risk of bias assessment

The risk of bias for each randomized controlled trial (RCT) included was assessed using the Cochrane's tool. This risk, classified according seven domains, listed on Figure 2, was independently assigned by two authors and discrepancies were resolved through discussions between them. The results were presented as risk of bias summary and risk of bias graph which were sketched using the software Review Manager 5.3 (Version 5.3.5).

Statistical analysis

Data statistical analysis was performed using Comprehensive Meta-Analysis software (Version 2.0).

The forest plot was generated to illustrate the study-specific RRs and the Weight Risk Ratio (WRR) estimate along with the 95% confidence intervals (CIs), using the random effects model. The I-squared statistic (I^2) was used as a measure of inconsistency across the findings of the studies.

Three different analyses were used to assess the potential impact of publication bias on the meta-analysis. One analysis is a funnel plot in which the log of RR was plotted against their corresponding standard error (SE). In the absence of publication bias, the studies will be symmetrically distributed about the WRR. Since its interpretation is largely subjective, Egger's regression test was also performed. Finally, the approach of Duval and Tweedie's Trim and Fill was also used. This approach uses an iterative

procedure to remove the most extreme small studies from the positive (or negative) side of the funnel plot, re-computing the RRs, yielding an unbiased estimate of WRR.

The sensitivity analysis was performed by removing each study at a time to evaluate the stability of the results. Furthermore, a subgroup analysis was made according to the mean age of patients, intervention duration, type and gender of patients.

Trial Sequential Analysis (TSA)

TSA is a methodology in which the evidence required is quantified, providing a value for the required information size (RIS). To adjust the CIs due to sparse data and repeated testing in cumulative meta-analysis, TSA program version 0.9.5.5 Beta was used. If the cumulative *Z*-curve crosses the trial sequential monitoring boundary or enters the futility area, then it can be concluded that a sufficient level of evidence for the anticipated intervention effect may have been reached and no further trials are needed. The TSA was performed at the level of an overall 5% risk of type I error and a power of 80%.

RESULTS

Included studies

Complying with the PRSIMA statement, the initial search identified 157 articles with potential to be included in this meta-analysis. Figure 1 shows the progression details of the database search regarding the effects of cranberries in the prevention of UTIs. After all the steps, 25 studies were considered suitable for performing qualitative and quantitative analyses. Among the reasons to exclude studies were absence of control group and lack of results in terms of the outcome of interest. From the 25 included studies, 3 were divided into 2 different trials, totalizing 28 studies (4947 patients) included in this meta-analysis. The work of Caljouw, et al 2014[3] was divided since it presents patients with high and low UTI risk. Stothers 2002[7] provided two different ways of oral administration of cranberry products: tablets of concentrated cranberry juice and pure unsweetened cranberry juice. Wing, et al 2008[8] administered two different doses of PACs: high dose (240 mg PACs/day) and low dose (80 mg PACs/day). During the search two previous meta-analyses, regarding the prevention of UTIs by cranberries, were also found.[5,6] The work of Jepson and Craig, 2012[5] focused on the effectiveness of cranberry and blueberry products preventing symptomatic UTIs,

and included 13 trials in the meta-analysis.[5] The study of Wang, et al 2012[6] evaluated cranberry-containing products for the prevention of UTI and examined the factors influencing their effectiveness, including 10 clinical trials.[6] The present meta-analysis includes 28 clinical trials, strengthening the statistical analysis which allows to better understand the effects of ingesting cranberries on the prevention of UTIs.

The list of studies included in this work and their characteristics are summarized in Table 1. All of them represented people who are at a certain risk of repeat UTI: children and elderly patients, long-term care facilities residents, cancer patients, patients with spinal cord injury, and patients with Clean Intermittent Catheterization (CIC). The follow-up of the included trials varies from 2-weeks to 12-months. The patients enrolled in the intervention groups were subjected to ingestion of cranberries in several different oral forms, ranging from juices, capsules, tablets, and extracts, with different dosages of PACs per day.

Risk of bias

The results of the assessment of risk of bias of the included RCTs are summarized in Figure 2. The studies of Bonetta and Di Pierro 2012[9] (nonrandomized), Burleigh, et al 2013[2] (observational study) and Ledda, et al 2015[10] (registry, supplement and pilot study) were not classified to their risk of bias since the Cochrane's tool can only be applied to RCTs. In general, the included RCTs satisfied the 7 domains of bias. The RCTs claimed to be randomized, but only 13 trials detailed the randomization process and are classified as "Low risk" in the random sequence generation domain. Concerning the performance and detection types of bias, related to blinding of participants and personnel, and blinding of outcome assessment, respectively, 3 studies were classified as "High risk", since the authors are not clear about the blinding process. Other sources of bias were also identified, namely the payment of a stipend to the participants in the trials or sponsorship and financial support, which are factors that can skew the results.

Effects of cranberries ingestion

The meta-analysis results are summarized in Table 2 and outlined in the forest plot of Figure 3. Overall, the estimated WRR showed a significant reduction in risk of repeat UTI with cranberry treatment when compared to placebo (WRR=0.6750; 95% CI:0.5516-0.7965; *p*-value<0.0001), with moderate degree of heterogeneity (I^2=58.1740%). The TSA was undertaken (Figure 4), resulting in a RIS of 4875, which

was reached, and the cumulative *Z*-curve crosses the boundaries. So, it is possible to reach a conclusion with no need of additional trials. To the best of our knowledge, TSA for the ingestion of cranberries on incidence of UTIs was for the first time applied, strengthening the conclusions now achieved.

Subgroup and Sensitivity analyses

To evaluate the influence of the mean age of patients, intervention duration, type and gender of patients, in the effectiveness of cranberries in the prevention of UTIs, a subgroup analysis was performed (Table 3).

Although there is evidence of the benefit of cranberries in reducing UTIs overall, the analysis of subgroups showed that compared with placebo, cranberries did not significantly reduce the occurrence of repeat UTIs for any of the subgroups: CIC (WRR=0.887; 95% CI:0.676-1.165; *p*-value=0.384), young and older adults (WRR=0.824; 95% CI:0.443-1.533; *p*-value=0.542 and WRR=0.833; 95% CI: 0.697-1.119; *p*-value=0.304), pregnant women (WRR=0.792; 95% CI:0.371-1.687; *p*-value=0.545) and patients with bladder or cervical cancer (WRR=1.150; 95% CI:0.747-1.796; *p*-value=0.526).

The sensitivity analysis was performed by excluding one or more studies from the analysis to see how this affected the results (Figure 5). This analysis showed that the pooled effects of cranberries ingestion on incidence of UTIs did not change substantially if a single or a few studies were omitted. Overall, the sensitivity analysis demonstrated that the findings of the present meta-analysis are robust.

Publication bias

The funnel plot, generated for the defined outcome and considering the Trim and Fill adjustment (Figure 6), includes both the observed studies (blue circles) and the necessary imputed studies (red circles) to obtain the absence of bias. There are more studies on the left than on the right, so 9 studies are imputed on the right to “adjust” the funnel plot for the absence of publication bias. The key finding, that the risk ratio is of substantive importance, did not change (WRR adjusted= 0.8334; 95%CI: 0.6976-0.9956). In addition to the visual inspection of the funnel plot, the presence of publication bias was explored using Egger’s regression test which did not indicate evidence of publication bias (Table 4).

DISCUSSION

Several studies demonstrated the effects of cranberries in subgroups of the population that are at increased risk of UTIs. This systematic review with meta-analysis demonstrates the effectiveness of cranberry products in the prevention of UTIs. The addition of further studies to previous meta-analyses allows to conclude that there exists a strong evidence that cranberries decrease the number of UTIs, particularly for patients with rUTIs.

Single UTI episodes are very common, especially in adult women, with a 50-fold higher rate of infection than adult men.[11] A subgroup analysis concerning the gender of patients was performed to verify if the effects of cranberries ingestion are gender-dependent. It was observed that for both genders the incidence of UTIs is significantly decreased in the cranberry-treated group.

It is known that the prevalence of UTIs is also age-dependent.[11] During the first year of life, UTIs are less than 2% and its incidence among males remains relatively low after 1-year of age and until approximately 60-years of age when enlargement of the prostate interferes with emptying of the bladder.[11] Taking this into consideration, a subgroup analysis concerning the mean age of patients was performed. The obtained results allow to conclude that for children (2-17 years) and for middle-aged adults (36-55 years) the cranberries ingestion reduces significantly the incidence of UTIs.

The results of subgroup analysis for type of patient revealed that patients with rUTIs and those that had undergone gynecological surgery were more protected by the intake of cranberries, with a significant reduction of the incidence of UTIs for those groups. This is an interesting result which reinforces the importance of the ingestion of cranberries by patients at some risk to develop UTIs.

Although the European Association of Urology (EAU) recommends the continuous use of cranberries as an alternative method for the prevention of UTIs, the data are not conclusive because the available studies have been conducted for periods of up to a year. So, there is no evidence to support the efficacy of cranberries products for chronic use. In future, trials may need to cover much longer periods.

Effectiveness of cranberry products is likely to be dependent on their concentration of PACs, the polyphenols associated with the amelioration of UTIs. The most accepted mechanism of action for the prevention of UTIs by cranberries, is based on its

interference with bacterial adhesion in the urinary tract.[12] An antiadhesion response is caused in urine after cranberry consumption, preventing uropathogenic P-fimbriated *E. coli* from adhering to bladder cell receptors.[12] If the bacteria are not able to adhere to cells, they cannot grow and cause infection.[12] The daily recommended amount of PACs in order to decrease the number of UTIs is at least 36 mg. A limitation of the findings is the lack of consistency among the administered dosages of PACs in the considered studies.

Another limitation founded during this manuscript preparation was the absence of uniformity in the definition of UTI among the included trials. All of them use the term UTI while in fact some of them are referring specifically to *E. coli* UTI. The differentiation between UTI and *E. coli* UTI does make a clinical difference; for example, cranberry would likely not be effective in patients with other uropathogens but it would be expected that it is effective in patients with *E. coli* UTI since cranberry inhibits the adhesion of pili from *E. coli*.

CONCLUSIONS

The present systematic review with meta-analysis could be used by physicians to recommend the ingestion of cranberries to reduce the incidence of UTIs, particularly for patients with recurrent UTIs. This alternative treatment could also help to reduce the widespread use of antibiotics that is leading to the worldwide emergence of antibiotic resistant microorganisms.

Future research should focus on clarifying the underlying mechanisms that contribute to the efficacy of cranberries' PACs in the reduction of UTIs and the standardization of quantities of cranberries and/or dosages of ingested cranberries' PACs along with the duration of the treatment required to be effective.

ACKNOWLEDGEMTS

Ângelo Luís acknowledges the Post-Doc research fellowship within the scope of the protocol signed between Universidade da Beira Interior and bank Santander/Totta with the reference BIPD/ICI-FC-BST-UBI 2016.

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Table 1: Characteristics of the included studies in this systematic review with meta-analysis.

Study	Year	Study design	Type of patient	Gender	Mean age	Intervention group	Control group	Design duration	Location	Dosage of PACs
Afshar, et al[13]	2012	randomized, controlled	toilet trained child 18 years old or younger with at least 2 culture documented symptomatic UTIs in the calender year before recruitment	Children (both genders)	7.0	cranberry juice containning 37% PACs	cranberry juice with no PACs	12-months	Canada	NA
Barbosa-Cesnik, et al[14]	2011	randomized, double-blind, placebo-controlled	women with ≥ 3 symptoms of UTI (painful and frequent urination, and report of either urgency, hematuria, or supra-pubic pressure), and would be in Ann Arbor for the next 6-months	Female	21.2	low-calorie cranberry juice cocktail	placebo juice	6-months	USA	224 mg/day
Bianco, et al[15]	2012	randomized, double-blinded, placebo-controlled	women with history of UTIs	Female	NA	cranberry capsules	placebo capsules	1-month	USA	324 mg/day
Bonetta and Di Pierro[9]	2012	nonrandomized	patients with prostatic adenocarcinoma, treated with radiotherapy to the prostatic area (and to the pelvis if the risk of limph node involvement was higher than 15% according to Kattan's nomograms)	Male	NA	*Vaccinium macrocarpon* (cranberry) standardized extract in an enteric-coated formulation	NA	6 to 7-weeks	Italy	60 mg/day
Burleigh, et al[2]	2013	observational study	women with a history of rUTIs, defined as at least 3 UTIs in the past year (subjects with 2 UTIs in the past 6-months but not 3 in the past year were also enrolled)	Female	37.0	sweetened, dried cranberries	NA	2-weeks	USA	NA
Caljouw, et al[3] **a) (High UTI Risk)**	2014	double-blind, randomized, placebo-controlled	long-term care facilities residents - high UTI risk (long-term catheterization, diabetes mellitus, at least one UTI in the preceeding year)	Both genders	84.0	cranberry capsules	placebo capsules	12-months	Netherlands	18 mg/day
Caljouw, et al[3] **b) (Low UTI Risk)**	2014	double-blind, randomized, placebo-controlled	long-term care facilities residents - low UTI risk	Both genders	84.0	cranberry capsules	placebo capsules	12-months	Netherlands	18 mg/day
Cowan, et al[16]	2012	randomized, double-blind, placebo-controlled	patients with cervical cancer about to start standard chemoradiation (chemotherapy plus radiation therapy) or patients with bladder cancer about to start standard radical radiotherapy	Both genders	68.3	cranberry juice	placebo beverage	6-weeks	UK	NA
Ferrara, et al[17]	2009	randomized, controlled	children with more than 1 UTI due to *Escherichia coli* in the last year before the begining of the study, without antimicrobial prophylaxis	Children (both	7.5	cranberry concentrate juice	NA	6-months	Italy	NA

				genders)						
Foxman, et al[18]	2015	randomized, double-blind, placebo-controlled	nonpregnant women, without a history of nephrolithiasis, congenital urogenital anomaly or neurogenic bladder, elective for gynecological surgery	Female	56.0	cranberry juice capsules	placebo capsules	2-months	USA	NA
Hess, et al[19]	2008	randomized, double-blind, placebo-controlled	subjects with a clinically documented spinal cord injury determined by a staff physician with documentation of neurogenic bladder	Male	53.0	cranberry extract tablet	placebo tablet	6-months	USA	NA
Kontiokari, et al[20]	2001	randomized, placebo-controlled	women with UTIs caused by *Escherichia coli* ($\geq 10^5$ colony forming units/mL in clean voided midstream urine) and were not taking antimicrobial prophylaxis	Female	30.5	cranberry-lingonberry juice	placebo juice	12-months	Finland	NA
Ledda, et al[10]	2015	registry, supplement and pilot study	subjects with a history of rUTIs (at least 3 symptomatic UTIs in the last year before inclusion or 2 UTIs in the last 6-months)	Both genders	39.0	capsules containing highly-standardized cranberry extract	lifestyle and hygiene advice	2-months	Italy	NA
Lee, et al[21]	**2007**	**randomized, double-blind, placebo-controlled**	**community dwelling patients with spinal cord injuries**	**Both genders**	**43.5**	**cranberry tablets**	**placebo tablets**	**6-months**	**Australia**	**NA**
Maki, et al[22]	2016	randomized, double-blind, placebo-controlled	healthy women with BMI<40 Kg/m^2 and with a recent history of a UTI, defined as ≥ 2 episodes of a UTI that were treated by a health care professional in the past year (self-report) of which ≥ 1 UTI has been treated ≤ 6-months of the screening visit	Female	41.0	cranberry beverage	placebo beverage	6-months	USA	119 mg/day
McGuinness, et al[23]	2002	randomized, double-blinded, placebo-controlled	multiple sclerosis patients with Expandend Disability Status Scale score between 0 and 8, with no indwelling or condom catheters, if using intermittent self-catheterization used standard technique and catheterized no more than 6 times daily, with some symptoms of neurogenic bladder and with no current UTI	Both genders	45.1	cranberry supplement	placebo	6-months	Canada	NA
McMurdo, et al[24]	2005	randomized, double-blind, placebo-controlled	patients aged 60 years or over	Both genders	81.4	cranberry juice	placebo beverage	35-days	UK	838 µg/day
Pagonas, et al[25]	2012	controlled	renal transplant outpatients with rUTIs who underwent prophylaxis	Both genders	54.5	cranberry juice	placebo juice	12-months	Germany	NA
Salo, et al[26]	2011	randomized, double-blind, placebo-controlled	children on account of verified UTI in the previous 2-months	Children (both genders)	4.2	cranberry juice	placebo juice	6-months	Finland	NA
Schlager, et al[27]	1999	double-blind,	children with neurogenic bladder receiving clean intermittent catheterization 4	Children	NA	cranberry juice	placebo juice	6-months	USA	NA

		placebo-controlled	times a day, living at home, had normal findings on renal ultrasonography and voiding cystourethrogram, and lived a 1-hour drive from hospital	(both genders)						
Singh, et al[28]	2016	randomized, placebo-controlled	patients with subclinical asymptomatic bacteriuria and/or rUTIs, not responding to antimicrobials	NA	38.7	cranberry capsules	lactobacillus capsules	3-months	India	120 mg/day
Stothers[7] **a) (Tablet)**	2002	randomized, double-blind, placebo-controlled	sexually active women with at least 2 symptomatic, single-organism, culture-positive UTI in the prior calendar year, but were currently free of UTI on urinalysis and culture	Female	41.5	tablet of concentrated cranberry juice	placebo tablet	12-months	Canada	NA
Stothers[7] **b) (Juice)**	2002	randomized, double-blind, placebo-controlled	sexually active women with at least 2 symptomatic, single-organism, culture-positive UTI in the prior calendar year, but were currently free of UTI on urinalysis and culture	Female	43.5	pure unsweetened cranberry juice	placebo tablet	12-months	Canada	NA
Takahashi, et al[29]	2013	randomized, double-blind, placebo-controlled	outpatients with acute exacerbation of acute uncomplicated cystitis or chronic complicated cystitis (including self-catheterization) who had a past history of multiple relapses of UTI and in whom healing by antimicrobial agents had been confirmed by expert urologists	NA	57.0	cranberry juice	placebo beverage	6-months	Japan	40 mg/day
Vostalova, et al[4]	2015	randomized, double-blind, placebo-controlled	women with medical history of at least 2 episodes of symptomatic UTIs in the previous 12-months	Female	36.8	cranberry fruit powder capsules	placebo capsules	6-months	Czech Republic	1.4 mg/day
Waites, et al[30]	2004	randomized, double-blind, placebo-controlled	community-residing men and women who were at least 1-year post-spinal cord injury with age ≥ 16 years and with neurogenic bladder managed by clean intermittent catheterization or external collection device	Both genders	41.0	concentrated cranberry extract	lactose placebo	6-months	UK	NA
Wing, et al[8] **a) (High Dose)**	2008	randomized, placebo-controlled	pregnant women at less than 16-weeks of gestation	Female	NA	low-calorie cranberry juice cocktail beverage	placebo beverage	6-weeks	USA	240 mg/day
Wing, et al[8] **b) (Low Dose)**	2008	randomized, placebo-controlled	pregnant women at less than 16-weeks of gestation	Female	NA	low-calorie cranberry juice cocktail beverage	placebo beverage	6-weeks	USA	80 mg/day

UTIs – urinary tract infections; rUTIs – recurrent UTIs; PACs – proanthocyanidins; BMI – body mass index; NA – not available.

Table 2: Effects of cranberries ingestion on incidence of UTIs.

Outcome	Number of trials	Number of patients	RIS	WRR observed (95% CI)	*p*-value	I^2 (%)	Model used	WRR adjusted (95% CI)
incidence of UTIs	**28**	**4947**	**4875**	**0.6750 (0.5516-0.7965)**	**<0.0001***	**58.1740**	Random	**0.8334 (0.6976-0.9956)**

UTIs – urinary tract infections; RIS – required information size; WRR – weighted risk ratio; CI – confidence interval; * Indicates a significant result.

Table 3: Subgroup analysis of the effects of cranberries ingestion on incidence of UTIs.

Variable	incidence of UTIs				
	Number of trials	References	95% CI	*p*-value	I^2 (%)
Total	**28**	**see Table 1**	-	-	-
WRR observed	-	-	**0.6748 (0.5716-0.7965)**	**<0.0001***	**58.174**
WRR adjusted	-	-	**0.8334 (0.6976-0.9956)**	-	-
Mean age (years)					
Children (2-17)	**4**	**13, 17, 26, 27**	**0.557 (0.353-0.880)**	**0.012***	21.289
Young adults (18-35)	**3**	**8, 14, 20**	0.824 (0.443-1.533)	0.542	58.447
Middle-aged adults (36-55)	**10**	**2, 4, 7, 10. 19, 22, 23, 25, 28, 30**	0.565 (0.449-0.711)	**<0.0001***	44.100
Older adults (>55)	**5**	**3, 7, 18, 24, 29**	0.883 (0.697-1.119)	0.304	24.610
Intervention duration (months)					
1-3	**8**	**2, 8, 9, 10, 15, 18, 24, 28**	0.574 (0.408-0.810)	0.002*	64.385
6	**11**	**4, 14, 17, 19, 22, 23, 26, 27, 29, 30, 21**	**0.766 (0.603-0.972)**	**0.003***	**54.272**
12	**5**	**3, 7, 13, 20, 25**	0.681 (0.515-0.900)	0.007*	42.339
Type of patient					
rUTIs	**15**	**2, 3, 4, 10, 13, 14, 15, 16, 17, 20, 22, 25, 26, 28, 29**	0.645 (0.523-0.796)	**<0.0001***	60.406
CIC	**6**	**3, 19, 23, 27, 30, 21**	**0.887 (0.676-1.165)**	**0.389**	**19.640**
Gynecological surgery	**1**	**18**	0.522 (0.279-0.975)	0.041*	0.000
Elderly patients	**1**	**24**	0.505 (0.209-1.224)	0.130	0.000
Prostatic adenocarcinoma	**1**	**9**	0.359 (0.214-0.612)	**<0.0001***	0.000
Bladder or cervical cancer	**1**	**16**	1.150 (0.747-1.769)	0.526	0.000
Pregnant women	**1**	**8**	0.792 (0.371-1.687)	0.545	0.000
Gender					

Male	**2**	**9, 19**	0.364 (0.232-0.571)	**<0.0001***	0.000
Female	**10**	**2, 4, 7, 8, 14, 15, 17, 18, 20, 22**	0.634 (0.488-0.823)	0.001*	50.155

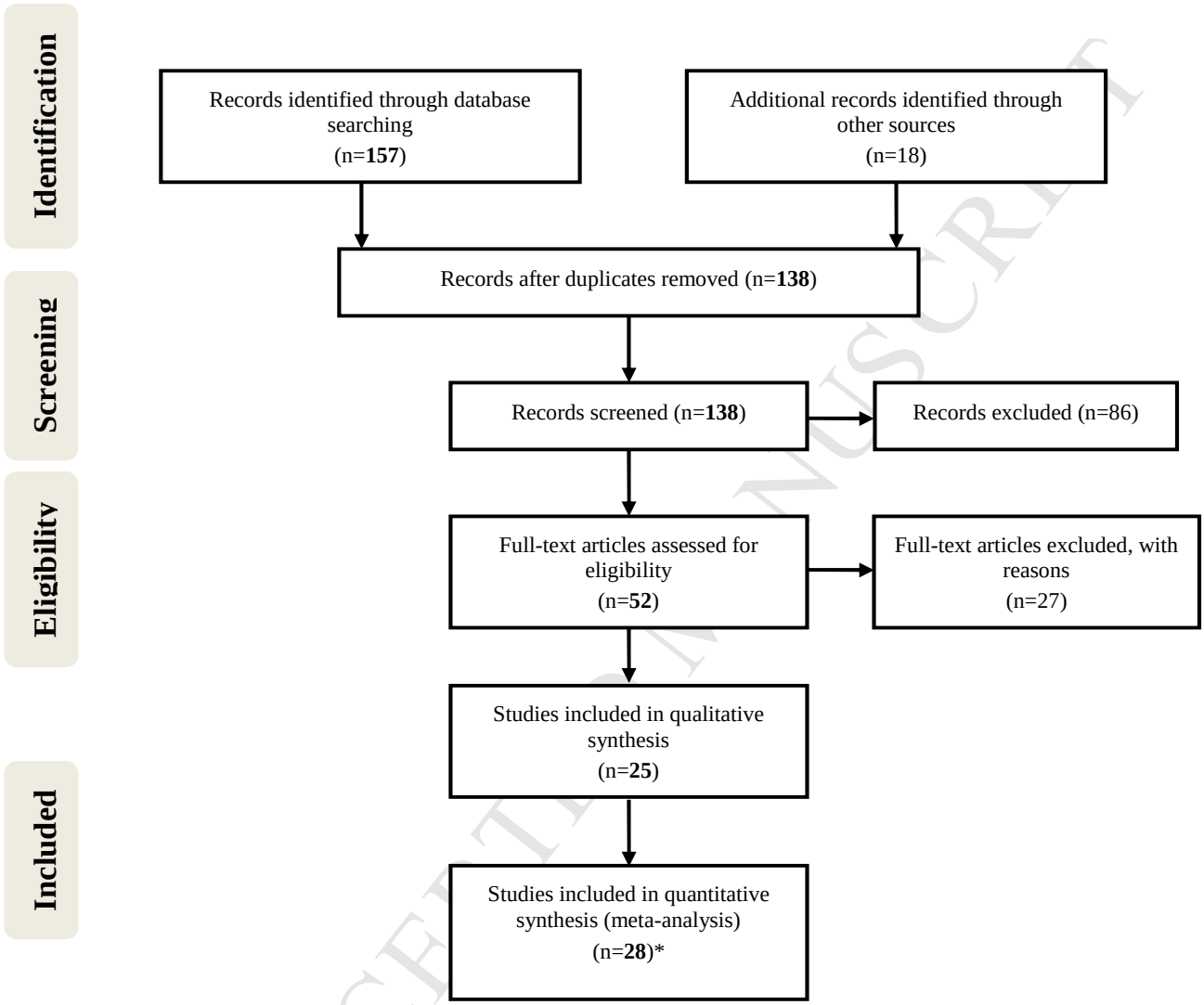
UTIs – urinary tract infections; rUTIs – recurrent UTIs; CIC – Clean Intermittent Catheterization; WRR – weighted risk ratio; CI – confidence interval; * Indicates a significant result.

Table 4: Assessment of publication bias for the impact of cranberries ingestion on incidence of UTIs.

Outcome	Egger's regression test			
	95% CI	***t***	**df**	***p*-value**
incidence of UTIs	**-2.81222 to 0.07500**	**1.94874**	**26**	**0.0623**

UTIs – urinary tract infections; CI – confidence interval; df – degrees of freedom.

Figure 1: Flow-diagram of database search, trial selection and articles included in this systematic review with meta-analysis.



*The works of Caljouw, et al 2014[3], Stothers 2002[7] and Wing, et al 2008[8] were divided into 2 different trial

Figure 2: Results of risk of bias assessment regarding the methodological quality of included studies: **A)** Risk of bias summary: review author's judgments about each risk of bias item for each included study; **B)** Risk of bias graph: review author's judgments about each risk of bias item presented as percentages across all included studies.

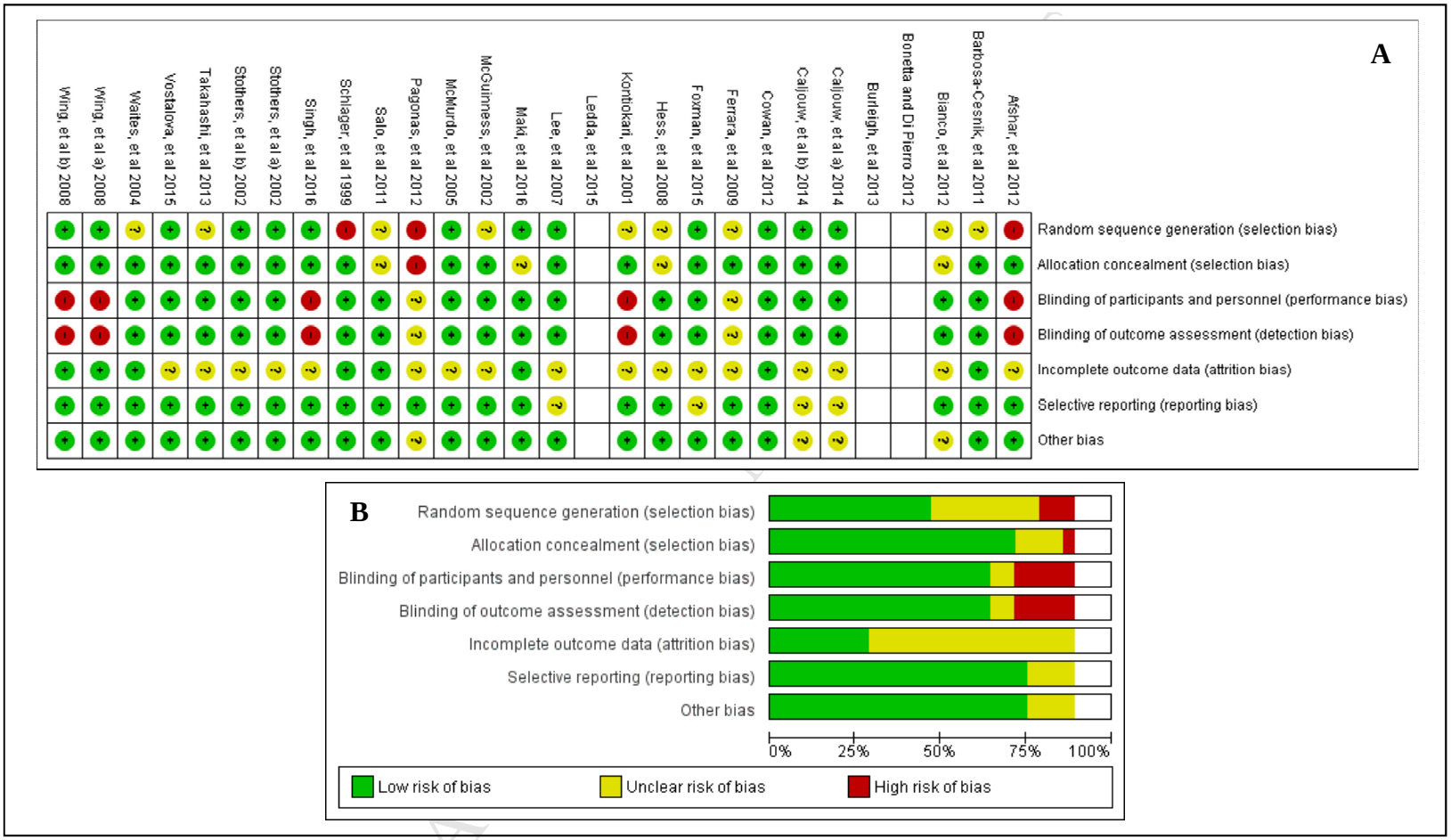


Figure 3: Forest plot of comparisons of the effects of cranberries ingestion on incidence of UTIs.

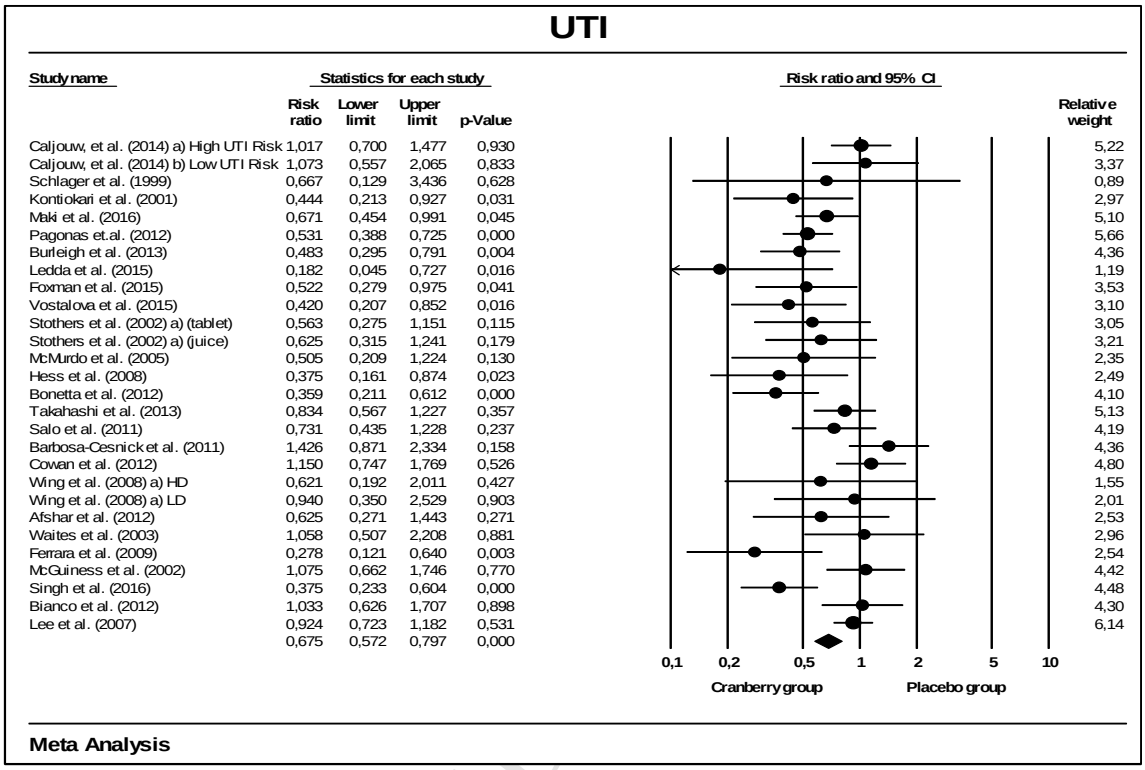


Figure 4: Trial Sequential Analysis on pooled result of the effects of cranberries ingestion on incidence of UTIs.

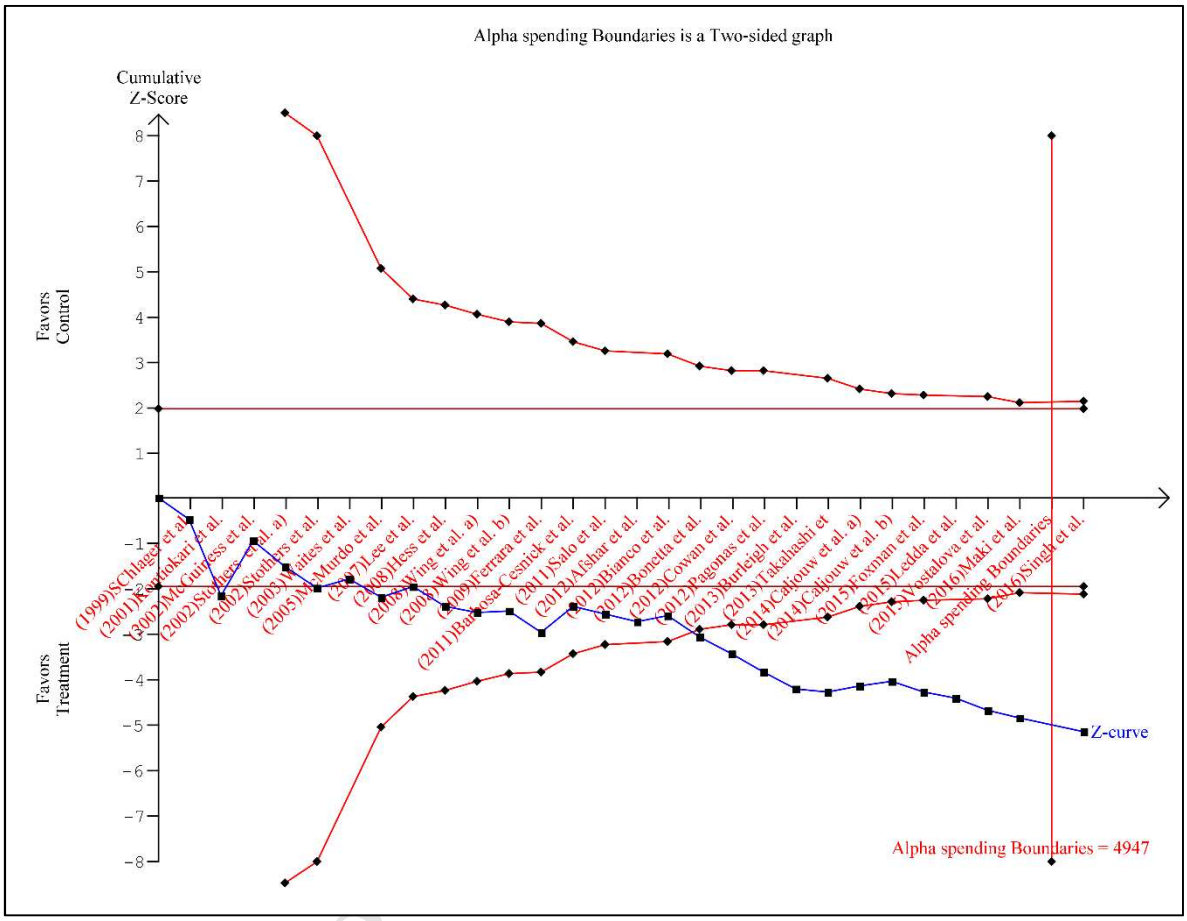


Figure 5: Results of sensitivity analysis.

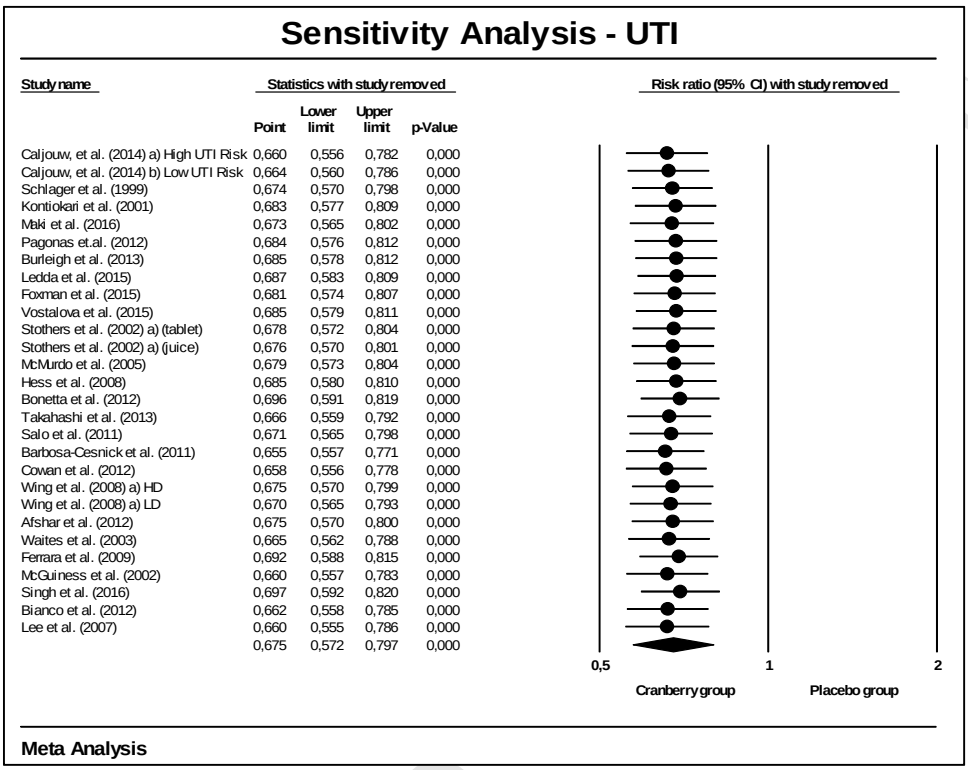
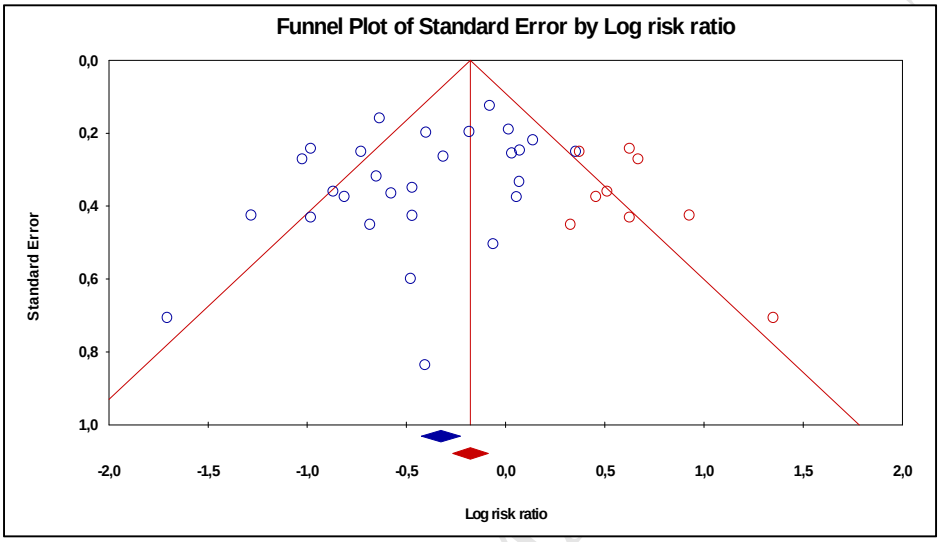


Figure 6: Funnel plot of standard error by log risk ratio (publication bias tests) of the effects of cranberries ingestion on incidence of UTIs.



Key of definitions for abbreviations

CI – confidence interval

CIC – clean intermittent catheterization

PAC – proanthocyanidin

RCT – randomized controlled trial

RIS – required information size

RR – risk ratio

rUTI – recurrent urinary tract infection

SE – standard error

TSA – Trial Sequential Analysis

UTI – urinary tract infection

WRR – weighted risk ratio