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Review Article

Effectiveness of herbal medicines to prevent and control symptoms of urinary tract infections and to reduce antibiotic use: A literature review

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ABSTRACT

Background: Antimicrobial resistance is a rapidly growing global issue affecting the effective treatment of infectious diseases. This provides a window of opportunity for the use and implementation of well researched effective complementary therapies such as herbal medicines. In this literature review, an overview is provided of the effectiveness of herbal medicine to control symptoms of urinary tract infections and reduce antibiotic use.

Methods: PubMed, CAM-Quest, CORE-Hom, ScienceDirect, CAMBase, Anthromedics.org and AnthroMedLibrary databases were searched for peer-reviewed meta-analyses, systematic reviews and randomized controlled trials from 2005 till 8 October 2020. Included were clinical studies on the use of herbal medicine for clinically diagnosed urinary tract infection with any control group except another herbal medicine. Study quality was assessed using the Joanna Briggs Institute critical appraisal tools.

Results: Of the 408 citations identified, 23 met the inclusion criteria: 5 meta-analyses, 3 systematic reviews and 15 randomized controlled trials. Of these studies 13 involved the use of cranberry products, 4 studies concerned traditional Chinese herbal medicines, and 6 studies dealt with other herbal medicines.

Conclusions: The latest published meta-analysis including 28 trials reports a clear benefit of Cranberry products for the prevention of recurrent UTIs in women. Five TCM formulas were found to be equally or more effective than antibiotics in the treatment of UTIs. Furthermore, Rosa canina seems to have the potential to prevent UTI in women undergoing a caesarean section. 'Acidif Plus Tablets' as well as 'Canephron' seem to be promising candidates for treating women with uncomplicated recurrent UTI.

1. Introduction

The rapid rise of antimicrobial resistance (AMR) is a global challenge affecting effective treatment of infectious diseases.[1,2] Currently, infections with multi-drug resistance bacteria are estimated to cause 25,000 deaths each year in the EU alone, resulting in €1.5 billion in health care expenditures and costs of productivity loss.[3] Global actions have been taken to address this urgent issue. In 2015 the WHO issued a Global Action Plan on AMR, which was followed in 2016 by the United Nations Political Declaration on AMR. The EU has set up a Joint Programming Initiative on AMR to coordinate research efforts across the world. Despite these efforts, antimicrobial resistance has increased significantly over the last years.[2]

Urinary tract infections are a very common infection for which people consult primary care physicians and receive antibiotics treatment.[4] Around half of all healthy women will experience at least one UTI during their life. 25–35% of those women will have a recurrence of UTI within the following year.[5] UTIs are the most common reason for antibiotics prescription in pregnant women.[6] UTIs frequently occur in clinical situations such as during chemotherapy, when using a catheter, with cases of urinary obstruction, immunosuppression etc.[7] Antibiotics are not only prescribed to treat UTIs but also prophylactic to prevent recurrence of UTIs.[8]

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Instead of using antibiotics as a strategy to fight UTIs, there are also treatment strategies that favour the strengthening of the immune system to be able to protect developing a UTI.[9] These resilience-based strategies are applied as self-care or prescribed by physicians in whole medical systems such as Traditional Chinese Medicine, Ayurveda, Anthroposophic medicine and naturopathy.[10] One of the promising strategies is the use of herbal medicine which combines antimicrobial activities of the constituents with stimulating resilience.[11] Since the rise of AMR will reduce the options for using antibiotics shortly, these other strategies become of more interest and should be researched carefully.

In this literature review, we discuss meta-analyses, systematic reviews and randomized controlled trials (RCTs) on herbal medicine used in several whole medical systems to treat or prevent UTIs across all populations. Such a broad review of all herbal treatments is an addition to existing reviews which are restricted to specific products or product groups, such as Cranberry products,[12] or restricted to certain populations.[13,14]

The objective of this literature review, therefore, is to provide an overview of the effectiveness of herbal medicines to control symptoms of urinary tract infections and reduce antibiotic use.

2. Methods

This review was prepared using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.

2.1. Search strategy

PubMed, CAM-Quest, CORE-Hom, ScienceDirect, CAMBase, Anthromedics.org and AnthroMedLibrary databases were searched for publications from 2005 till 8 October 2020 (the past 15 years). The search terms used in PubMed were ((herbal medicine[MeSH Terms]) OR (phytotherapy[MeSH Terms]) OR (medicine, traditional[MeSH Terms]) OR (Chinese medicine, traditional[MeSH Terms]) OR (medicine, ayurvedic[MeSH Terms]) OR (naturopathy[MeSH Terms]) OR ((homeopathy [MeSH Terms]) OR (anthroposophy[MeSH Terms])) AND (urinary tract infections[MeSH Terms]). In ScienceDirect a similar search string was used: "urinary tract infections" AND ("herbal medicine" OR "phytotherapy" OR "traditional medicine" OR "Chinese medicine" OR "ayurvedic medicine" OR "homeopathy" OR "anthroposophy") AND "meta-analysis". The Anthromedics.org, AnthroMedLibrary, CAM-Quest, CORE-Hom and CAMBase databases were searched using the term 'urinary tract infections'. Since anthroposophic medicines are not always allocated to specific indications in scientific literature, the Vademecum of anthroposophic medicine was consulted to find the most used AMPs for UTI. Based on this consultation a further search of PubMed, CAM-Quest, and Anthromedics.org was conducted using the search term 'Argentum nitricum comp.'.

2.2. Eligibility criteria

All peer-reviewed literature published in the last 15 years was included, including meta-analyses, systematic reviews and randomized controlled trials. Meta-analysis and systematic reviews of observational studies were excluded. Participants of any age, ethnicity or gender were included with a clinically diagnosed urinary tract infection during the study or in the past (prevention studies), which is defined as a presumptive diagnosis of UTI based on symptoms and signs rather than on laboratory investigations or medical imaging. Studies in which UTIs were artificially induced were excluded.

All studies describing herbal medicine such as western herbal medicine, traditional Chinese medicine, Ayurvedic medicine, and anthroposophic herbal medicine were included, with or without a prescription of delayed antibiotics. The herbal medicines could contain any number of herbs, dosages, administration forms, durations of use. Herbal medicine is defined as "product derived from plants used raw or refined for treatment of disease".[15]

The clinical studies described in the sources could contain any of the following control groups: (1) an inactive treatment (placebo or no treatment), (2) an active non-CAM treatment (standard care, or antibiotics). Clinical studies could also compare an active intervention with or without herbal medicine as an add on. Studies comparing two different CAM or herbal medicine treatments were excluded.

Only publications written in Dutch, English, French and German were included. Although the literature in the last 15 years was searched, a stepped approach was used to analysis the data. First, meta-analysis were identified. If one or more meta-analyses were available for a specific herbal medicine these were included, older systematic reviews or RTCs were not included in the analysis. Then the researcher would check for more recent systematic reviews and RCTs concerning the particular herb and include them in the analysis. If no meta-analysis was available, systematic reviews were identified and included. In addition, RCTs not covered by the systematic review and more recent RCTs were included. If no systematic reviews were available, RCTs over the last 15 years were included in the analysis.

2.3. Data collection and analysis

A single researcher identified the literature, screened the titles and abstracts and subsequently the full texts and decided on eligibility for inclusion in the analysis. All relevant data was extracted by one researcher and corrected by another researcher into an Excel spreadsheet. The following study items were extracted from meta-analyses and systematic reviews: author, year of publication, search range, intervention, study population, comparators, outcomes (including effect sizes), number of trials, sample size per trial, quality rating. From individual RCTs the sample size, age range, country of the study, intervention duration, and outcome measures were extracted in addition to the items mentioned for the meta-analyses and systematic reviews. The outcomes of this literature review were either prevention of UTI in the case of studies using herbal medicines to prevent recurrence or occurrence of UTI, or treatment of UTI. Any method for assessing these outcomes were allowed.

2.4. Quality appraisal

Two researchers evaluated the quality of the meta-analyses, systematic reviews and RCTs. The quality of the meta-analyses and systematic reviews was assessed using the Joanna Briggs Institute critical appraisal tool for systematic reviews.[16] Consensus was reached through discussion of discrepancies between the assessors. Systematic reviews and meta-analyses were judged to be of 'high quality' when more than 75% of the criteria were positively rated ($\geq$7 items), 'medium quality' when between 50–74% were positively rated (6 and 7 items), and 'low quality' when $<$50% were positively rated (0–5 items). The quality of the individual RCTs was assessed using the Joanna Briggs Institute critical appraisal tool for RCTs.[17] RCTs were judged to be of 'high quality' when more than 75% of the criteria were positively rated ($\geq$ 9 items), 'medium quality' when between 50–74% were positively rated (7 and 8 items), and 'low quality' when $<$50% were positively rated (0–6 items).

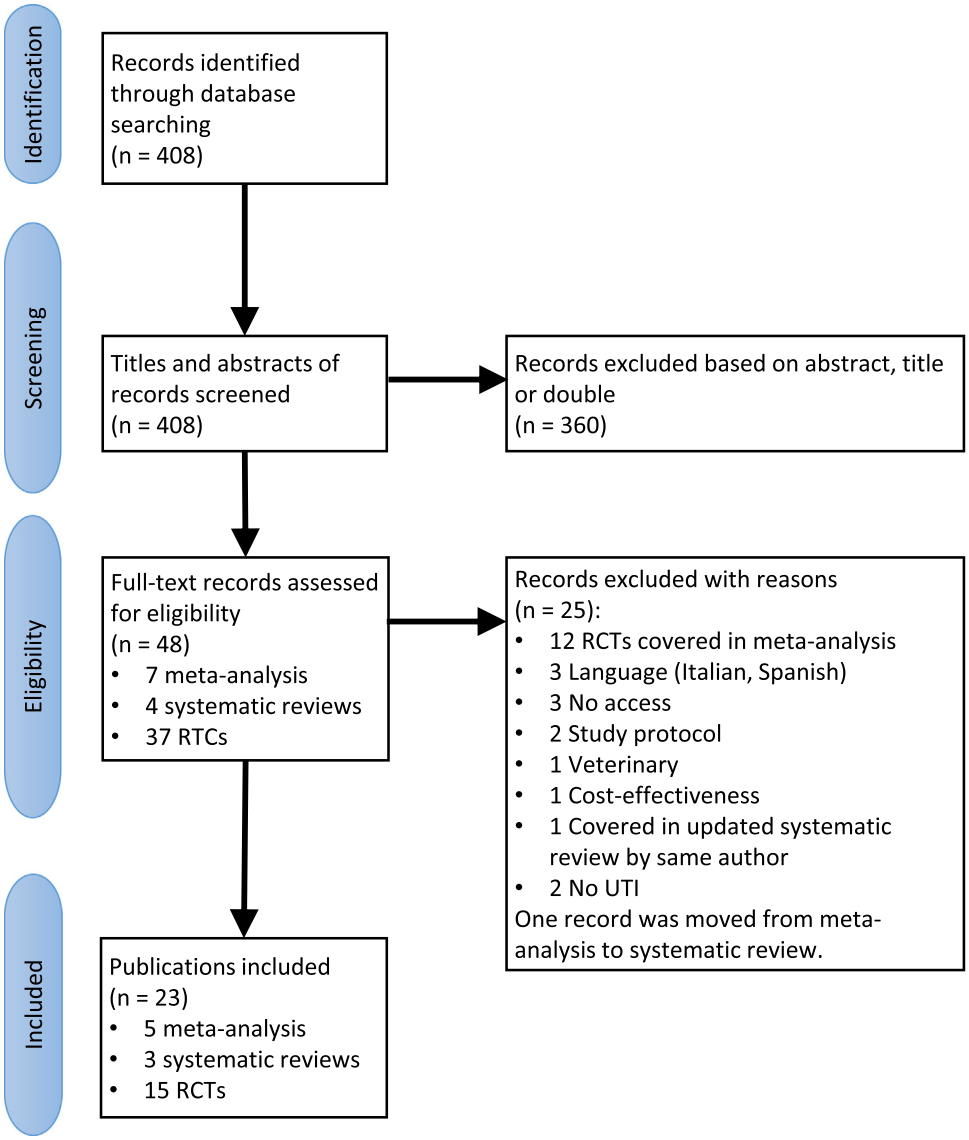

Fig. 1. PRISMA flow diagram of search results.

3. Results

3.1. Study selection

In total 408 records were identified in the databases of which 360 were excluded based on title, abstract or existing twice in the list of records. The full texts of 48 records were assessed for eligibility, these records were obtained from PubMed (n = 35), CAM-Quest (n = 11) and ScienceDirect (n = 2). In total 25 full text records were then excluded for reasons described in Fig. 1, of which 12 were RCTs covered in the meta-analyses and systematic reviews (Table 1). Included in the analysis were 23 publications, of which 5 were meta-analyses,[14,18–21] 3 were systematic reviews[12,13,22] and 15 were RCTs.[23–38] A summary of the study characteristics of the included studies is presented in a separate table for the systematic reviews (Table 2) and the RCTs (Table 3).

3.2. Quality assessment

Fig. 2 shows the results of the quality appraisal of the meta-analyses and systematic reviews using the JBI quality appraisal tool. Most of these meta-analyses and systematic reviews included RCTs only, excluding studies with other study designs. This is unfortunate, since especially in the area of complementary and herbal medicine there is restricted funding for RCTs.[12,18–22] Other study designs need to be taken into account to get a full picture. Furthermore, none but one publication[21] included an extensive number of CAM related sources into the search strategy, such as CAMBase, CAM-Quest, Anthromedics.org. Jepson et al. included one large study with negative results into the analysis but didn't explain the heterogeneity that might be caused by studies with cranberry product containing too low levels of PAC.[19] Overall, four studies were of high quality,[13,14,20,21] two of medium quality[18,19] and two of low quality.[12,22]

Fig. 3 shows the results of the quality appraisal of the randomized controlled trials using the JBI quality appraisal tool. One of the high quality studies was funded by the industry.[28] In the study by Wan et al. the placebo for the cranberry juice consisted of tomato juice with sugar, which is easy to identify and therefor doesn't constitute a good placebo control.[29] Overall, eleven of the RCTs were of high quality,[23,25,28,29,31–37] two were of medium quality[26,38] and two of low quality.[24,30]

Table 1.
Randomized controlled trials included in the 5 meta-analyses.

Author year (ref)	Jepson 2012[19]	Wang 2012[20]	Flower 2015[21]	Luis 2017[18]	Smith 2018[14]
McMurdo 2005[39]	v	v		v	v
Albrecht 2007[40]					v
Lee 2007[41]	v			v	
Wing 2008[42]	v	v		v	
Beerepoot 2011[43]	v				v
Afshar 2012[44]	NA	NA		v	
Takahashi 2013[45]	NA	NA		v	
Caljouw 2014[46]	NA	NA		v	
Foxman 2015[47]	NA	NA	NA	v	
Vostalova 2015[48]	NA	NA	NA	v	v
Maki 2016[49]	NA	NA	NA	v	
Singh 2016[50]	NA	NA	NA	v	v

NA, not applicable (studies were published after the search date).

	Luis 2017	Jepson 2012	Wang 2012	Smith 2018	Flower 2015	Ghouri 2018	Liska 2016	Durham 2015
1. Is the review question clearly and explicitly stated?	-	+	+	+	+	+	+	?
2. Were the inclusion criteria appropriate for the review question?	-	+	-	+	+	+	-	-
3. Was the search strategy appropriate?	?	+	+	+	+	+	+	+
4. Were the sources and resources used to search for studies adequate?	-	-	-	-	+	-	-	-
5. Were the criteria for appraising studies appropriate?	+	+	+	+	+	+	-	-
6. Was critical appraisal conducted by two or more reviewers independently?	+	+	+	+	+	+	-	-
7. Were there methods to minimize errors in data extraction?	+	+	+	+	+	-	-	-
8. Were the methods used to combine studies appropriate?	+	+	+	+	+	+	+	na
9. Was the likelihood of publication bias assessed?	+	-	+	-	+	na	-	-
10. Were recommendations for policy and/or practice supported by the reported data?	+	-	+	-	+	+	+	+
11. Were the specific directives for new research appropriate?	+	-	+	+	+	+	+	+
Overall quality (H=High, M=Medium, L=Low)	**M**	**M**	**H**	**H**	**H**	**H**	**L**	**L**

Fig. 2. Quality appraisal of the meta-analyses and systematic reviews.

	Cai 2018	Liu 2019	Wagenlehner 2018	Zhang 2005	Gallien 2014	Gunnarsson 2017	Juthani-Mehta 2016	Letouzey 2017	Occhipinti 2016	Wan 2016	Seifi 2018	Moore 2019	Katz 2014	Larmo 2008	Temiz 2018
1. Was true randomization used for assignment of participants to treatment groups?	?	+	+	-	+	+	+	+	+	+	+	+	+	+	+
2. Was allocation to treatment groups concealed?	?	+	+	-	+	-	-	?	?	+	+	+	?	+	+
3. Were treatment groups similar at the baseline?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
4. Were participants blind to treatment assignment?	?	+	+	-	+	+	+	+	+	-	+	+	+	+	-
5. Were those delivering treatment blind to treatment assignment?	?	+	+	-	+	+	+	+	?	+	+	+	+	+	-
6. Were outcomes assessors blind to treatment assignment?	?	?	+	-	+	?	?	+	+	+	+	+	?	?	-
7. Were treatment groups treated identically other than the intervention of interest?	+	+	+	+	+	+	+	+	-	+	?	+	+	+	+
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	+	-	+	?	+	+	+	-	+	+	-	+	+	+	+
9. Were participants analyzed in the groups to which they were randomized?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
10. Were outcomes measured in the same way for treatment groups?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
11. Were outcomes measured in a reliable way?	?	?	?	?	+	?	+	+	?	+	?	+	+	+	+
12. Was appropriate statistical analysis used?	?	+	+	?	+	+	+	+	+	+	+	+	-	+	+
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-
Overall quality (H=High, M=Medium, L=Low)	**L**	**H**	**H**	**L**	**H**	**H**	**H**	**H**	**M**	**H**	**H**	**H**	**H**	**H**	**M**

Fig. 3. Quality appraisal of the randomized clinical trials.

4. Discussion

4.1. Cranberry products

The most recent meta-analysis on the use of cranberry for prevention of recurrent UTI shows a significant reduction in the risk of repeat UTIs compared to placebo (weighted RR 0.675, 95% CI 0.55–0.80, $p < 0.0001$) based on 28 clinical trials with a total of 4947 patients.[18] The authors report moderate heterogeneity ($I^2 = 58\%$) which is in line with observations in other meta-analyses with fewer and less recent studies which has resulted in mainly negative findings. A notable one is the Cochrane review by Jepson et al. in 2012 concluding that cranberry products do not reduce the incidence of rUTI.[19] The authors report that the inclusion of the Barbosa-Cesnik[51] study into the meta-analysis introduced substantial heterogeneity. At the same time Wang et al.[20] conducted a meta-analysis also observing the large heterogeneity that would be introduced by adding the Barbosa–Cesnik study. Jepson et al. decided to keep the study into the meta-analysis resulting in a negative conclusion regarding cranberry use, while Wang et al. excluded the study resulting in a positive conclusion regarding cranberry use. The reason for the heterogeneity introduced by

Table 2.
Summary of the meta-analyses and systematic reviews.

Author year (ref)	Search range	Intervention	Population	Comparators and outcomes	N of trials (N of subjects)
Meta-analyses					
Luis 2017[18]	Inception to September 2016	Cranberry	General population	*Cranberry* vs. *Placebo, no treatment, other* Reduced repeat UTIs (WRR 0.68, 95% CI 0.55–0.80) *Subgroup analyses cranberry* vs. *placebo* Clean intermittent catheterization: no effects (WRR 0.89, 95% CI 0.68–1.17) Young adults: no effects (WRR 0.82, 95% CI 0.44–1.53) Older adults: no effects (WRR 0.83, 95% CI 0.70–1.12) Pregnant women: no effects (WRR 0.79, 95% CI 0.37–1.69) Bladder or cervical cancer: no effects (WRR 1.15, 95% CI 0.75–1.80)	28 studies (4974)
Jepson 2012[19]	Inception to July 2012	Cranberry	General population	*Cranberry* vs. *Placebo or no treatment* No difference in repeat UTI (RR 0.86, 95% CI 0.71–1.04) Women with rUTI : no reduction in risk of repeat UTI (RR 0.74, 95% CI 0.42–1.31) Older men and women: no prevention of UTI (RR 0.75, 95% CI 0.39–1.44) Patients needing catheterisation : no reduction in UTI (RR 0.95, 95% CI 0.75–1.20) Pregnant women: no reduction of UTI (RR 1.04, 95% CI 0.93–1.16) Children with susceptibility to UTI: no prevention of UTI (RR 0.48, 95% CI 0.19–1.22) *Cranberry compared with antibiotic prophylaxis* Women with rUTI: equal effect in reducing risk of repeat UTI (RR 1.31, 95% CI 0.85–2.02) Children: equal effective in reducing risk of repeat UTI (RR 0.69, 95% CI 0.32–1.51)	13 RCTs (2462) 5 RCTs (594) 2 RCTs (413) 2 RCTs (353) 2 RCTs 2 RCTs 2 RCTs 1 RCT
Wang 2012[20]	Inception to November 2011	Cranberry containing products	General population	*Cranberry* vs. *control* Effective in prevention of UTI (RR 0.62, 95% CI 0.49–0.80) *Subgroup analyses* Women with rUTI: effective (RR 0.53, 95% CI 0.33–0.83) Female populations: effective (RR 0.49, 95% CI 0.34–0.73) Children: effective (RR 0.33, 95% CI 0.16–0.69) Cranberry juice drinkers: effective (RR 0.47, 95% CI 0.30–0.72) Subjects using cranberry products 2x daily: effective (RR 0.58, 95% CI 0.40–0.84)	10 studies (1494) 2 studies 4 studies 1 study 5 studies 4 studies
Smith 2018[14]	Inception to September 2017	Any treatment of prevention strategy	healthy women with recurrent UTI	*Cranberry* Jepson 2008: cranberry more effective than placebo (RR 0.62, 95% CI 0.40–0.97) Jepson 2012: no reduction in rUTI (RR 0.74, 95% CI 0.42–1.31) Wang 2012: prevention of rUTI (RR 0.53, 95% CI 0.33–0.83) Fu 2017: reduced RTI risk by 26% (RR 0.74, 95% CI 0.55–0.98) Beerepoot 2016: decrease rUTI (RR 0.53, 95% CI 0.33–0.83) *TCM* (See results Flower 2015 below)	74 studies 2 studies 24 studies (4473) 3 RCTs 7 studies (1498) 2 studies (250) 7 studies (542)
Flower 2015[21]	AMED 1937 to November 2014 CBM from 1978 CNKI from 1979 VIP from 1989 Wan Fang from 1990	Chinese herbal medicines	recurrent UTI in adult women	*TCM* vs. *antibiotics* TCM significanty more effective (RR 1.21, 95% CI 1.11 - 1.33) TCM fewer episodes of UTI (RR 0.28, 95% CI 0.09–0.82) *TCM + antibiotics* vs. *antibiotics* TCM significanty more effective (RR 1.24, 95% CI 1.04 - 1.47) TCM fewer episodes of UTI (RR 0.53, 95% CI 0.35–0.80) Er Xian Tang vs. San Jin Pian Er Xian Tang more effective (RR 1.28, 95% CI 1.03–1.57) Er Xian Tang fewer episodes of UTI (RR 0.40, 95% CI 0.21–0.77)	3 studies (282) 2 studies (120) 1 study (80)
Systematic reviews					
Ghouri 2018[13]	Inception to July 2017	non-antibiotic prevention measures	Pregnant women	Hygiene behaviours are associated with UTI incidence. Immunisation might be beneficial for preventing UTI in women. No evidence to support effect of cranberry in prevention of UTI.	2 RCTs (948)
Liska 2016[12]	Not reported	Cranberry	Healthy women	Effect of cranberry for rUTI prevention differs across populations.	9 SRs
Durham 2015[22]	1966 to June 2015	Cranberry	Paediatric patients	Cranberry might be effective in prevention of UTI in otherwise healthy children. At least as effective as antibiotics in children with underlying urogenital abnormalities	8 RCTs

Table 3.
Summary of the randomized controlled trials.

Author	Population	N	Country	Age (M, range)	Intervention	Comparator	Intervention duration	Outcome measures	Outcomes
Antibiotics control group									
Cai 2018[24]	women with uncomplicated rUTI from 1 referral centre	93	Italy	46,8 (22–63)	Acidif Plus tablet (400 mg L-Methionine, 100 mg *Hibiscus sabdariffa*, 100 mg *Boswellia serrata* (L.) Roxb.) orally twice daily	short term antibiotic therapy according to trialist's choice based on the EAU guidelines on urological infections	1 week	Urinary pathogens $< 10^3$ CFU/mL in urine at 30 and 90 days, symptom scores, QoL	Clinical improvement and QoL improved in both groups ($p < 0.001$), at 90 days more improvement in intervention group ($p < 0.003$). More transitions from UTI to ABU in intervention group at day 90 ($p = 0.007$).
Liu 2019[36]	Women with rUTI (≥3 in last year $>10^5$ CFU/ml) and clinical symptoms (dysuria, frequent urination, and/or urgency)	122	China	54,8 ± 17,0	Bazheng powder 116 g granules (15 g *Anemarrhena aspodeloides* Bunge, 10 g *Platycladus orientalis* (L.) Franco, 10 g *Angelica sinensis* (Oliv.) Diels, 15 g *Rehmannia glutinosa* (Gaertn.) DC, 15 g *Poria cocos* (Schw.) Wolf, 10 g *Salvia miltiorrhiza* Bunge, 6 g *Theum palmatum* L., 10 g *Polygonum aviculare* L., 10 g *Dianthus superbus* L., 15 g *Talcum)* twice daily	Levofloxacin 200 mg granules twice daily or Amoxicillin/clavulanic acid 500 mg granules 3 times daily for 1 week, then 3 weeks placebo granules	4 weeks	Clinical recovery Uropathogen clearance, incidence of UTI recurrence, hepatorenal function. Disease recurrence after 6 months	Both groups equal numbers of clinical cure, equal uropathogen clearance and UTI recurrence rate. Higher cure % in CM group than AB group $p < 0.05$. Symptomatic improvement higher in AB group than CM group $p < 0.05$. Treatment efficacy 90.2% in CM group and 82.0% in AB group, $p > 0.05$.
Wagenlehner 2018[28]	Women with uncomplicated UTI symptoms sum score ≥6 (dysuria, pollakisuria and urgency) + leukocyturia + reported on the Acute Cystitis Symptom Score (ACSS)	659	Germany (16), Ukraine (22), Poland (13)	44.3 (18–74)	2 coated tablets Canephron (18 mg *Centaurii herba,* 18 mg *Levistici radix,* 18 mg *Rosmarini foliu*) 3 times daily plus placebo granules on day 1	granules of fosfomycin trometamol (3 g fosfomycin) dissolved in 100–200 mL water on day 1 plus placebo tablets 3 times daily	7 days	Ratio of need for antibiotics during 30 days. Acute uncomplicated cystitis symptoms, QoL and changes after therapy (ACSS) on day 4, 8, and 38, bacteruria, leukocyturia.	Less AB use in Canephorn group -6.26%, 95% CI −11.99–0.53, $p = 0.0014$, not inferior to AB group. Comparable decrease in ACSS scores. More bacteruria in Canephorn group at end of treatment ($p = 0.028$). No differences in leukocyturia, paracetamol use, adverse events. In both groups majority did not take additional AB between Day 1 and 38 (primary outcome). Difference non-AB (−6,3%) lies within the non-inferiority margin of 15%.
Zhang 2005[30]	Subjects with UTI	256	China	(3–76)	Antibiotics plus 2–3 capsules of Zishen Tongli Jiaonang (*Flos Chrysanthemi Indici, Rhizoma Smilacis Glabrae, Semen Plantaginis, Herba Taraxaci, Herba Scutellariae Barbatae, Radix Achyrantis Bidentatae*) orally 2 and 3 times daily	Antibiotics: cefradine, ofloxacin or other, according to drug sensitivity. Orally taking or intravenous drip. Drinking water	2 weeks	Remission rates after a two-course treatment and recurrence rates after one year. Complete remission (negative leukocyte and bacteruria tests)	Less recurrence in treatment group (4.4% versus 30%), $p < 0.01$. More complete remission in treatment group (72.1% versus 55.8%), $p < 0.05$.

(*continued on next page*)

Table 3. (*continued*)

Author	Population	N	Country	Age (M, range)	Intervention	Comparator	Intervention duration	Outcome measures	Outcomes
Placebo control group									
					Cranberry products				
Gallien 2014[31]	stable MS patients with pollakiuria, urgency, dysiria or urinary incontinence from 8 outpatient settings in university hospitals or rehabilitation centers	171	France	49 ± 10	Cranberry extract powder (18 mg proanthocyanidins) twice daily for 1 year	Placebo powder	1 year	Time to first symptomatic UTI. 1-year UTI rate. At month 3, 6, 9 and 12: QoL (Qualiveen scale), EDSS score, symptoms, number of MS relapses, antibiotic consumption, side effects.	No difference in time to first UTI, 1-year UTI rates. QoL score at month 9 was higher in placebo group ($p = 0.02$). No differences in other endpoints.
Gunnarsson 2017[23]	female patients with hip fracture and pre-operative indwelling urinary catheter	144	Sweden	82,8 ± 8,7	2 capsules of NurtiCran (550 mg cranberry powder) twice daily, starting 30 min before catherization	Placebo capsules	5 days	Positive urinaty culture (1 col $>10^4$ cfu/mL) at day 5 or 14 postoperatively, clinical symptoms of UTI, Euro Qual.	No difference in hospital acquired positive culture in 5 days ($p = 0.270$) or 14 days ($p = 0.826$).
Juthani-Mehta 2016[32]	Females in multiple long-term care homes	185	USA	86,4 ± 8,2	2 capsules of cranberry (36 mg proanthrocyanidis) once daily	Placebo capsules	360 days	Presence of bacteriuria (1 or 2 col 10^5 cfu/mL) and pyuria every 2 months. UTI symptoms, death, hospitalisation, antibiotic resistant organisms, antibiotics.	No difference in bacteriuria over 12 months ($p = 0.98$). No differences in rate of death, hospitalization, multi-drug resistant bacetria, antibiotics use.
Letouzey 2017[35]	patients receiving transurethral catheterisation after pelvic surgery	272	France	58,5 (45–68)	36 mg cranberry (PAC) once daily	Placebo	10 days	Bacteruria within 15 days ($>10^3$ CFU/ml). Bacteruria within 40 days. E. coli infections by day 15 and day 40.	No differences in bacteruria within 15 days RR 1.05, 95% CI 0.78–1.4, $p = 0.763$. No differences in bacteruria within 40 days.
Occhipinti 2016[38]	Women and men with at least 2 culture-documented symptomatic UTIs in the past year	70 (60 female, 10 male)	Italy	38	Cranberry extract capsules 500 mg (Oximacro 112 mg, microcrystalline cellulose 383 mg, magnesium stearate 5 mg) twice daily	Placebo, twice daily	7 days	Effect scores (0–10).	Significant more effect in cranberry group for females $p < 0.001$, and men $p = 0.016$.
Wan 2016[29]	Uncircumcised and circumcised boys with uncomplicated UTI from pediatrics and urology outpatient clinic of Renai and Zhongxing, Taipei.	55 uncircum-cised, 12 circumcised	Taiwan	9.5	120 mL North American cranberry, Ocean Spray Cranberries juice daily	120 mL placebo juice (diluted tomato juice with sugar)	6 months	Symptomatic UTI (bacteruria $\geq 10^5$ CFU)	Cranberry juice group lower incidence of UTI (25% versus 37%), $p < 0.05$.
					Other herbal medicinal products				
Seifi 2018[25]	Women undergoing cesarean section in Alzahra and Taleghani hospital in Tabriz.	400	Iran	30,2 ± 5,8	500 mg Rosa canina capsules, twice daily	Placebo	2 days after CS till 20 days after	Incidence of UTI at 7–10 and 20 days. Incidence of asymptomatic bacteriuria, cystitis, and pyelonephritis at 7–10 and 20 days.	Risk of asymptomatic UTI larger in placebo group at 7–10 days OR 3.37, 95% CI 1.08–10.54, $p < 0.001$; also at 20 days OR 6.74, 95% CI 1.96–23.19, $p < 0.001$. Total risk of UTI larger in placebo group at 7–10 days OR 0.22, 95% CI 0.07–0.67, $p = 0.006$; and at 20 days OR 0.32, 95% CI 0.14–0.75, $p = 0.008$.

(*continued on next page*)

Table 3. (*continued*)

Author	Population	N	Country	Age (M, range)	Intervention	Comparator	Intervention duration	Outcome measures	Outcomes
Moore 2019[37]	Women with uncomplicated acute UTI	382	UK	43,8 ± 15,36	Uva-ursi (20% arbutin) 1200 mg + ibuprofen 1200 mg, Uva-ursi 1200 mg + no ibuprofen, 3 times daily	Placebo + ibuprofen 1200 mg, Placebo + no ibuprofen	3–5 days	Mean frequency symptom severity score days 2–4. Mean unwell symptom severity score days 2–4. duration of bad or worse symptoms, mean global symptom severity score, use of antibiotics and reconsultation.	No difference in mean frequency symptom severity between uva-ursi and placebo groups
Katz 2014[33]	men with moderate to severe lower urinary tract symptoms at screening	40	USA	56,8 ± 2,25	4 capsules (2 × 2) of 500 mg AssuriTEA Men's Health (arm 1), 1000 mg AssuriTEA Men's Health (arm 2) daily (AMH contains green and black tea extract: min 40% total polyphenols, min 20% total catechins and theaflavins, 7–14% epigallocatechin-3-gallate, max 12% caffeine)	Placebo capsules	12 weeks	American Urological Association symptom score, BL, week 6 and 12. CRP, FRAP, CAP-e. Urologial measures. SF-36, IIEF at BL, week 6 and 12.	No differences in AUA scores between groups. Decrease of AUA-score in the 1000 mg group between baseline and 12 weeks. Less CRP increase at week 12 ($p = 0.048$). Qmean increased at week 6 ($p = 0.003$) and 12 ($p = 0.025$). Blood pressure decrease in 500 mg ($p = 0.020$) and 100 mg ($p = 0.003$) group at week 6. 1 AE in 500 mg AMH group, unrelated to treatment. 1 AE in 500 mg AMH group, possibly related to treatment.
Larmo 2008[34]	healthy men and women	233	Finland	19–50	28 g frozen H. rhamnoides spp. mongolica (Ostrobothnia, Finland) once daily	Placebo	90 days	Number and duration of daily symptoms of common cold (CC), digestive tract infections (DTI), UTI or other infection. Daily health status (yes/no). Nasal swab and serum in case of CC. Blood sample for CRP.	No difference in number of infections CC: RR 1.15, 95% CI 0.90–1.48; DTI: RR 1.06, 95% CI 0.67–1.68; UTI: RR 0.87, CI 0.44–1.70. No difference in duration of infections CC: RR 1.05, 95% CI 0.87–1.27; DTI: RR 1.08, 95% CI 0.82–1.43; UTI: RR 0.63, 95% CI 0.37–1.08. No difference in health status RR 1.06, 95% CI 0.76–1.49. CRP rises less vs. placebo at 3 months $p = 0.039$.
No intervention control group									
Temiz 2018[26]	Patients with urostomy ondergoing ileal conduit diversion in a hospital in Istanbul	60	Turkey	63.8 ± 4.7	1) Cranberry capsules (440 mg cranberry, 1.8% proanthocyanidins (9 mg)) twice daily. 2) training on UTI	No intervention	1 month after discharge for 3 months	Weekly reported UTI signs. Lab analysis at 2, 3 and 4 months.	No difference in mean urine pH between groups at 2 and 4 months $p > 0.05$. Mean urine pH higher in control group than cranberry group $p < 0.05$, and higher in training group than control group $p < 0.05$. No differences in mean white blood cell count and CRP levels. Cranberry reduced UTI incidence compared to no intervention $p = 0.01$. No difference in UTI incidence between cranberry and training group $p = 0.27$, and training and no intervention $p = 0.15$.

the Barbosa–Cesnik study was suggested to be the lower threshold of 10^3 CFU/mL for including patients, compared to the common threshold of 10^5 CFU/mL.[12] The most recent meta-analysis by Luis et al.[18] shows a positive effect of cranberry on prevention of rUTI compared to placebo even though the Barbosa-Cesnik study was included.

Subgroup analysis of specific populations have been performed in some of the meta-analyses. No significant effects of cranberry products were found for pregnant women, children, patient undergoing catheterization and patients with bladder or cervical cancer in the most recent meta-analysis by Luis et al.[18] Liska et al. report on differences in populations included in meta-analysis and suggests a larger effect of cranberry products for women with uncomplicated recurrent UTIs versus women with complicated UTIs.[12] Wan et al. show a reduction of UTI incidence in boys from a paediatrics clinic in Taiwan.[29] Ghouri et al. report on two RCTs with pregnant women using cranberry juice for the prevention of UTIs versus placebo showing potential effectiveness but with several limitations.[13] No effects of cranberry use on the presence of bacteriuria have been found in long-term care residents.[32] Recent RCTs indicate no effects of cranberry products on UTI incidence in female patients with hip fractures,[23] and in patients receiving transurethral catheterisation after pelvic surgery.[35]

Jepson et al. report equal effects of cranberry products versus antibiotics on the reduction of rUTI in women as well as children.[19]

Although there seems to be disagreement on the effect of Cranberry product on the prevention of recurrent UTIs in women, the latest meta-analysis based on 28 clinical trials with a total of 4947 patients[18] concludes with a clear positive effect. Analysis of subgroups such as children, pregnant women, and women undergoing surgery still results in mixed conclusions about effectiveness as well as differences in types of Cranberry products used. Larger studies with optimal conditions and clear inclusion criteria such as the dose and type of Cranberry product used are needed to obtain better insights.

4.2. Chinese herbal medicines

There is one Cochrane systematic review including seven RCTs with a total of 542 women on the use of Traditional Chinese Medicine for the prevention of rUTI.[21] TCM was found to have a significant higher rate of effectiveness for treating acute UTI compared with antibiotics (RR 1.21, 95% CI 1.11–1.33). Furthermore, TCM use resulted in significant fewer episodes of rUTI compared with antibiotics (RR 0.28, 95% CI 0.09–0.82). These result were based on three RCTs covered in the Cochrane review in which various TCMs were used as intervention: 1) Ma et al. 2011 used Qing Re Jie Du Tiao Gan Tang (*Bupleurum chinense* DC.(Chai Hu) 10 g, *Scutellaria baicalensis* Georg. (Huang Qin) 15 g, *Polygonum cuspidatum* Willd. ex Spreng. (Hu Zhang) 15 g, *Verbena officinalis* L. (Ma Bian Cao) 15 g, Talcum (Hua Shi) 15 g, *Dianthus superbus* L. (Qu Mai) 15 g, *Lophatherum gracile* Brongn (Dan Zhu Ye) 6 g, Paris *polyphylla* var. *yunnanensis* (Franch.) Hand-Mazz. (Cao He Che) 15 g, *Forsythia suspensa* (Thunb.) Vahl (Lian Qiao) 15 g, *Hedyotis diffusa* Willd. (Bai Hua She She Cao) 15 g, Semen *Plantago asiatica* L. (Che Qian Zi) 20 g, *Paeonia lactiflora* Pall. (Bai Shao) 20 g, *Curcuma aromatica* Salisb. (Yu Jin) 15 g, *Glycyrrhiza uralensis* Fisch. (Sheng Gan Cao) 10 g) twice daily for four weeks, 2) Shen et al. 2007 used Bai Tou Weng Tang and Er Xian Tang (*Anemone chinensis* Bunge (Bai Tou Weng) 15 g, *Phellodendron amurense* Rupr. (Huang Bai) 15 g, *Coptis chinensis* Franch. (Huang Lian) 6 g, *Fraxinus chinensis* subsp. *rhynchophylla* (Hance) A.E.Murray (Qin Pi) 12 g, *Anemarrhena asphodeloides* Bunge (Zhi Mu) 15 g, *Curculigo orchioides* Gaertn. (Xian Mao) 6 g, *Epimedium grandiflorum* var. *thunbergianum* (Miq.) Nakai (Xian Ling Pi) 6 g, *Angelica sinensis* (Oliv.) Diels (Dang Gui) 9 g, *Morinda officinalis* F.C. How (Ba Ji Tian) 9 g.) twice daily for four weeks, 3) Zhao et al. 2011 used a formula containing *Bupleurum chinense* DC. (Chai Hu) 10 g, *Gardenia jasminoides* J.Ellis ((Zhi) Zhi Zi) 10 g, *Citrus reticulata* Blanco (Qing Pi) 10 g, *Lindera aggregata* (Sims) Kosterm. (Wu Yao) 10 g, *Dianthus superbus* L. (Qu Mai) 15 g, Talcum (Hua Shi) 10 g, *Smilax glabra* Roxb. (Tu Fu Ling) 20 g, *Hedyotis diffusa* Willd. (Bai Hua She She Cao) 30 g, Herba *Plantago asiatica* L. (Che Qian Cao) 10 g, *Rehmannia glutinosa* (Gaertn.) DC. (Shu Di Huang) 10 g, *Lycium chinense* Mill. (Gou Qi Zi 15 g), *Epimedium grandiflorum* var. *thunbergianum* (Miq.) Nakai (Xian Ling Pi) 10 g, *Poria cocos* (Schw) (Fu Ling) 10 g, *Atractylodes macrocephala* Koidz (Chao Bai Zhu) 15 g, *Angelica sinensis* (Oliv.) Diels (Dang Gui) 12 g, *Glycyrrhiza uralensis* Fisch. (Zhi Gan Cao) 10 g twice daily for four months.

An RCT from Liu et al. 2019 reports equal effects of Bazheng powder compared with Levofloxacin or Amoxicillin/clavulanic acid on curing UTI.[36] Zhang et al. 2005 show less recurrence of UTI in the antibiotics plus Zishen Tongli Jiaonang group compared to the antibiotics only group ($p < 0.01$) as well as more complete remission ($p < 0.05$).[30] No placebo controlled studies with TCMs were found.

Summarizing, the recent meta-analysis of Flower et al. shows that there is substantial potential for finding herbal medicine to treat UTIs in Traditional Chinese Medicine.[21] At least five TCM formulas containing multiple herbs have been studied in RCTs with comparable or better effects than antibiotics treatment.[21] Probably there is a wealth of additional studies in Chinese language that are currently not critically assessed.

4.3. Other herbal medicine

Four placebo controlled randomized studies with various other herbal medicine as the active intervention were included in this literature review which were all of high quality.[25,33,34,37] Rosa canina capsules twice daily reduced the incidence of asymptomatic UTIs (after 7–10 days OR 3.37, 95% CI 1.08–10.54, $p < 0.001$; after 20 days OR 6.74, 95% CI 1.96–23.19, $p < 0.001$) as well as total risk of UTI (after 7–10 days OR 0.22, 95% CI 0.07–0.67, $p = 0.006$; after 20 days OR 0.32, 95% CI 0.14–0.75, $p = 0.008$) in women undergoing caesarean section in Iran.[25] 1200 mg of Uva-ursi 3 times daily did not seem to have an effect on mean frequency symptom severity scores at day 2–4 compared to placebo in women with uncomplicated UTI.[37] Four capsules of 500 mg or 1000 mg AssuriTEA Men's Health daily administration to men with moderate to severe lower urinary tract symptoms did not lead to significant changes in symptom scores, but blood pressure decreased in both the 500 mg ($p = 0.020$) and 1000 mg ($p = 0.003$) groups.[33] 28 g of *H. rhamnoides* spp. mongolica daily did not lead to differences in incidence of infections, duration of infections and health status after 90 days in healthy men and women.[34]

Two further studies were found comparing herbal medicines with an antibiotics control group.[24,28] Women with uncomplicated rUTI taking Acidif Plus Tablets containing 400 mg L-Methionine, 100 mg *Hibiscus sabdariffa*, 100 mg *Boswellia serrata* (L.) Roxb. twice daily for 1 week resulted in clinical improvement and improvement of quality of life, comparable with the antibiotics group.[24] However after 90 days the improvement of quality of life was stronger in the herbal medicine group ($p < 0.003$). Additionally, there were more transitions from UTI to asymptomatic bacteriuria in the herbal medicine group at day 90 ($p = 0.007$). Women with uncomplicated UTI taking 2 tablets of Canephron (containing 18 mg Centaurii herba, 18 mg Levistici radix, 18 mg Rosmarini foliu) 3 times daily for seven days resulted in less antibiotics use during the 30 day follow up period (−6.26%, 95% CI −11.99–0.53, $p = 0.0014$). However, this reduction in antibiotics use was comparable to the abtibiotics control group. There was

even more bacteriuria in the Canephron group at the end of the treatment period ($p = 0.028$).

Summarizing, *Rosa canina* has great potential for use with caesarean section to prevent UTI. Acidif Plus Tablets containing L-Methionine, *Hibiscus sabdariffa, Boswellia serrata* (L.) Roxb as well as Canephron containing *Centaurii herba, Levistici* radix, *Rosmarini* folium seem to be promising candidates for treating women with uncomplicated recurrent UTI.

4.4. Safety

One meta-analysis included in this study raises concerns about ingesting large volumes of cranberry juice with high sugar content for diabetic patients and refers to observations of gastrointestinal upset.[20] The systematic review by Durham reports that cranberry products are generally well tolerated, however, sweetened cranberry products should be used with caution in children with overweight or diabetes. Large doses of cranberry juice, 3 to 4 litres per day, may cause diarrhoea, and cranberry tables may increase urinary excretion of oxalate and other lithogenic ions and must be used with caution in persons prone to nephrolithiasis.[22] Most individual RCTs included in the review don't mention or don't report adverse events or report equal amounts of side effects from taking cranberry product as from taking the placebo. Use of cranberry products during pregnancy appears to be safe.[52] In the Norwegian Mother and Child Cohort Study the use of cranberry products was not found to be harmful during pregnancy.[53]

The Cochrane review on Chinese herbal medicines reports two studies mentioning specifically that no adverse events were found.[21] Side effects of other herbal medicines were not reported, or reported to be not significant, or reported to be less frequent than the antibiotics control group, or unrelated to the treatment.

Limitations of the study are the restriction to studies in Dutch, German, English and French while the search results indicate a possible large body of relevant studies in the Chinese or Korean language. Furthermore, a single researcher identified the literature, screened the titles and abstracts and subsequently the full texts and decided on eligibility for inclusion in the analysis. This study is significant in that it shows promising effective herbal medicines for the prevention and treatment of recurrent UTIs, indicating that herbal medicines can be used as alternative treatment and prevention options for UTIs instead of antibiotics.

4.5. Conclusion

This systematic review indicates positive effects of cranberry products, TCM formulas and other herbal medicines on prevention and treatment of recurrent UTIs in women. Herbal medicines are therefore promising options for reducing antibiotics use in the treatment and prevention of recurrent UTIs in women. Larger studies with optimal conditions and clear inclusion criteria such as the dose and type of Cranberry product used as well as studies on subgroups are needed to obtain more insights.

Author contributions

HAW and EvdW conceived the project idea. HA and NS collected and assessed the data. Data interpretation was conducted by HAW. HAW wrote the manuscript. All authors (HAW, EvdW, NS and EB) reviewed, commented on and approved on the final manuscript.

Conflict of interest

None of the authors declare any competing interests.

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Ethical statement

This review did not require an ethical approval.

Data availability

All data is included in the publication. There is no additional data available.

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