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Current clinical status on the preventive effects of cranberry consumption against urinary tract infections

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ABSTRACT

Urinary tract infections (UTIs) represent a common and quite costly medical problem, primarily affecting the female population which may be due to a shorter urethra. The bacterium *Escherichia coli* are mainly responsible for most uncomplicated UTIs. Cranberry antibacterial effects have widely been studied in vitro, and laboratory and clinical studies have also been performed to elucidate the mechanisms of cranberry actions and the clinical benefits of cranberry consumption against UTIs. The present review aimed to summarize the proposed mechanisms of cranberry actions against UTIs and the clinical trials that evaluated the efficacy of supplementing cranberry products in different subpopulations. Taking into consideration the existing data, cranberry consumption may prevent bacterial adherence to uroepithelial cells which reduces the development of UTI. Cranberry consumption could also decreasing UTI related symptoms by suppressing inflammatory cascades as an immunologic response to bacteria invasion. The existing clinical trials suggest that the beneficial effects of cranberry against UTIs seem to be prophylactic by preventing the development of infections; however, they exert low effectiveness in populations at increased risk for contracting UTIs. Additional well-designed, double-blind, placebo-controlled clinical trials that use standardized cranberry products are strongly justified in order to determine the efficiency of cranberry on the prevention of UTIs in susceptible populations.

1. Introduction

Simply stated, a urinary tract infection (UTI) refers to the presence of a certain threshold number of bacteria in the urine, usually 10^5 colony forming U/mL. This condition consists of either cystitis (bacteria in the bladder), urethral syndrome, or pyelonephritis (infection of the kidneys). Although UTIs can occur in both men and women, they are about 50 times more common in adult women compared to adult men, likely due to the presence of a shorter urethra in women [1]. Even more troublesome, UTIs are often recurring: 26.6% of women with a UTI were confirmed to have a second infection within 6 months. The first step for most UTIs is the colonization of periurethral tissues with uropathogenic organisms and then followed by the passage of the bacteria through the urethra. The bacteria proliferate in the otherwise

Abbreviations: UTI, urinary tract infection; *E coli*, Escherichia coli; PACs, proanthocyanidin polymers; UA, ursolic acid; HCA, hydroxycinnamic; HBA, hydroxybenzoic acid; NO, nitric oxide; COX-2, cyclooxygenase-2; TNF-α, tumor necrosis factor-α; LPS, lipopolysaccharide; TMP, trimethoprim; SMX, sulfamethoxazole.

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sterile urinary tract and then adhere to the bladder wall [2]. The bacterium, *Escherichia coli*, is responsible for most of the uncomplicated UTIs. Alarmingly enough, low-dose antibiotic prophylaxis that is currently recommended for preventing UTIs is related to the development of resistance to the causative microorganisms and the indigenous flora. In this aspect, the increasing prevalence of uropathogens, especially *E coli*, that are resistant to antimicrobial agents has stimulated interest in novel non-antibiotic methods for the prevention of UTIs [3].

Cranberries, also referred to as *Vaccinium macrocarpon*, consist of nearly 90% water and are great sources of dietary flavonoids, including anthocyanins and proanthocyanins (PACs) [4]. Augmenting evidence has suggested that cranberries may exert a preventive and therapeutic role in human UTIs. Based on promising in vitro data, several investigators started laboratory and clinical studies to determine the exact mechanism of action, as well as the clinical benefits of cranberry consumption in the management of UTIs. Herein, we aimed to review the basic mechanisms of action of cranberries against UTIs and to summarize current clinical trials that have evaluated their efficacy in the treatment of UTIs in different subpopulations. For this purpose, the Cochrane Library, PubMed, Embase, and Scopus databases were searched for relevant studies using keywords relating to cranberry and UTIs until May 2013 without restrictions and by reviewing the reference lists from retrieved articles.

2. Cranberry phytochemical composition

The chemical composition of the cranberry fruit family, which includes the American species, *V macrocarpon* and the European species, *V oxycoccus* (or *Northern cranberry* and *V microcarpum* or *small cranberry*), has recently been analyzed and several components have been isolated and identified in various fractions. Among them, the flavonoids anthocyanins, flavonols and PACs, catechins or flavan-3-ols, phenolic acid derivatives, and triterpenoid analogues have been identified as the major constituents of the cranberry species (Fig. 1).

The major anthocyanins in cranberries are galactosides and arabinosides of cyanidin and peonidin, and to a lesser extent, malvidin, pelargonidin, delphinidin, and petunidin [5,6]. Apart from monomeric anthocyanins, polymeric anthocyanin-containing color compounds seem to exist in cranberry non-dialyzable material [7]. Moreover, flavonols are found in abundance in cranberry fruits, mostly in glycosylated forms of quercetin, myricetin, isorhamnetin, and kaempferol. Prurin, a flavanone derivative, has been identified, isolated, and characterized in the cranberry fruit [7]. Flavan-3-ols, which are monomers of PACs, and several catechin derivatives have also been reported to exist in cranberries [8,9]. Notably, PACs have been quantified according to the degree of polymerization and not individually. In cranberry fruit they are primarily dimers, trimers, and larger oligomers of epicatechin. They also tend to occur as tetramers to decamers reaching to 23 degrees of polymerization composed of epicatechin units with epigallocatechin and catechin extending units [10]. PACs characterization in cranberry juice cocktail has shown the presence of a series of polyflavan-3-ol oligomers, composed of 4–10 repeating unit structures of epicatechin and epigallocatechin [11].

Cranberry fruit also contains triterpenoid derivatives of the ursane type. The major terpene in cranberries is the pentacyclic triterpene, ursolic acid (UA). UA content of whole cranberry fruit of different cultivars ranges between doses of 60-110 mg/100 g [12]. Two hydroxycinnamic derivatives in whole cranberry fruit in quantities that can average about 15 mg/100 g fresh fruit have mainly been reported [13]. Several sterols, iridoid glycosides, and other terpene derivatives have been isolated from whole cranberry fruit [14]. In addition, the cell wall composition of the cranberries seems to include a number of complex carbohydrates like pectin, cellulose, and hemicellulose [15]. Cranberries contain various sugars like sucrose, glucose, fructose, and sorbitol. Interestingly, apart from the presence of vitamin C in cranberries, a wide variety of vitamins and provitamins have been identified [7,16].

Another family of compounds includes derivatives of hydroxycinnamic and hydroxybenzoic acid in quantities that average about 15-20 mg/100 g fresh fruit and, to a lesser extent, derivatives of salicylic, ellagic, and benzoic acid [12]. The presence of high levels of ellagitannins has been reported, while unusually high levels of benzoates and simple phenolics were verified in cranberry juice, mostly in bound forms in the cell wall polysaccharides or esterified to sugars [17]. Resveratrol, a phenolic, stilbenoid compound with a similar chemical structure compared to the synthetic estrogen agonist diethylstilbestrol, has been isolated at a concentration of 900 ng/g dry weight in cranberry fruits from Nova Scotia (*V macrocarpon*) [18].

3. Cranberry mechanisms of action against UTIs: in vitro evidence

Preliminary studies, aiming to investigate the potential effects of cranberries in UTI prevention and management, have focused on the acidification of urine that was supposed to be caused by cranberry consumption. In the early 1900s, Blatherwick et al reported a reduction in urine pH level (6.4-4.5) with a concomitant increase in excretion of hippuric acid (0.77-4.74 g) after consumption of cooked cranberries. Similarly, several other investigators documented that certain amounts of cranberry juice (450-720 mL daily) lowered urinary pH [19,20]. However, none of the urine samples was bacteriostatic against *E coli*. However, Bodel et al documented that hippuric acid was bacteriostatic at a minimum concentration of 0.02 mmol/L at pH 5.0, while the antibiotic activity of hippuric acid decreased 5-fold as the pH increased to 5.6 [21]. Consequently, it was speculated that cranberry juice could not exert a bacteriostatic effect, since it was not rich enough in hippuric acid and, therefore, did not lower urine pH sufficiently [21]. Afterward, additional investigators confirmed these notions, it is now currently accepted that low concentrations of benzoic acid present in the fruit (0.1% of weight), along with the limited amount of cranberry that can be consumed daily, may rarely result in adequate hippuric acid excretion to achieve bacteriostatic urinary concentrations [22]. In other

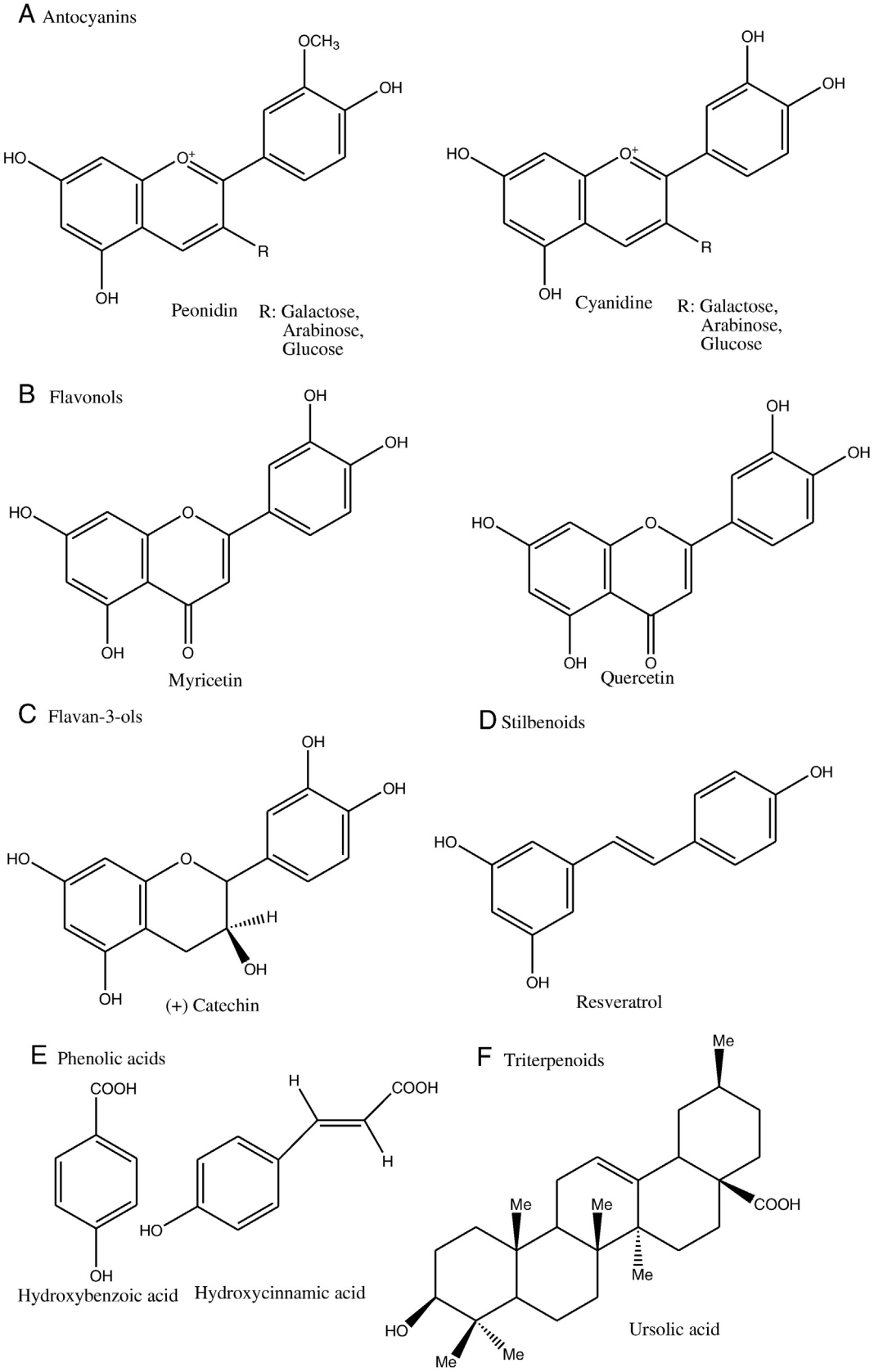

Fig. 1 – Molecular structure of representative compounds found in cranberries (prepared by ChemDrawn Ultra 9.0).

words, large amounts of cranberry juice are recommended in order for a slight reduction of urine pH and a moderate increase of hippuric acid excretion to be achieved. These changes are considered inadequate to confer significant antibacterial activity to urine. As a result, the theory of urine acidification as a mechanism of cranberry action against UTI has currently been disproved.

After taking into consideration the fact that bacterial adherence to mucosal surfaces is generally considered an important prerequisite for colonization and infection several investigators focused their research upon the anti-adhesion effects that cranberries have on certain urinary bacteria [23]. Interestingly, Sobota et al were the first to report that cranberry juice cocktail reduced ex vivo the adherence of clinical isolates of *E coli* originated from patients with UTI [24]. Fifteen of 22 patients showed significant anti-adherence activity in their urine 1-3 h after drinking 15 oz (443.6 mL) of cranberry juice cocktail [24]. Additional studies later confirmed the link between cranberry anti-adherent properties and its efficacy in preventing UTIs (Fig. 2). In this aspect, the anti-adherence ex vivo action of cranberry against strains of *E coli* was verified and strikingly demonstrated to be dose-dependent in a placebo-controlled, double-blind clinical trial by Di Martino et al [25]. In fact, as little as a 250 mL daily intake of cranberry juice cocktail inhibited adhesion to uroepithelial cells by 45%, while 750 mL reduced adhesion by 63% [25].

It is currently well-established that *E coli* has hair-like protruding fimbria on their surface that produces 2 adhesins (mannose sensitive and mannose resistant) through which the bacteria attach to specific receptors on uroepithelial cells [26]. Notably, these adhesins have been shown to be inhibited by 2 different cranberry compounds: (*i*) fructose, which suppresses the mannose-sensitive fimbrial adhesins and (*ii*) PAC, a high-molecular-weight compound that inhibits the mannose-resistant adhesins of uropathogenic *E coli* [27,28]. However, it should be noted that the first situation may only occur in vitro, since fructose is broken down in the metabolic process and does not reach the urine intact in vivo. Moreover, the presence of the first anti-adhesive compound fructose is not restricted to cranberry but represents the main ingredient of many other fruits. However, PAC, especially A-linked PAC, is a unique compound that is only found in juices from *Vaccinium* berries and exerts anti-adhesion effects of P-fimbriated uropathogenic *E coli* to uroepithelial cells (i.e. cranberries and blueberries) [29]. In contrast, B-linked PAC is found in grapes, apples, green tea, and dark chocolate and lacks such anti-adhesion activities [30]. It should also be noted that although PACs exert very strong anti-adhesive effects against urinary isolates of *E coli*, it has only moderate anti-adherent activity against fecal *E coli* isolates [28,31].

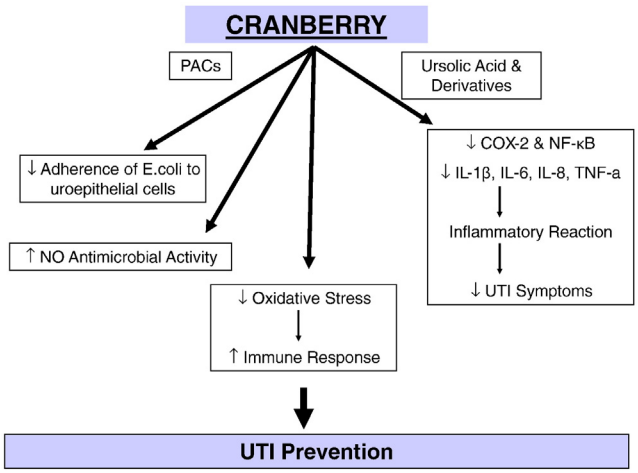

Fig. 2 – Potential Mechanisms of action explaining cranberry beneficial effects on UTIs. COX-2, cyclooxygenase-2; NF-κB; nuclear factor κ light-chain enhancer of activated B cells.

The anti-adhesive properties of cranberries are considered to contribute to UTI prevention not only through direct prevention of *E coli* adherence to uroepithelial cells, but also via selection of less adherent bacterial strains in the stool [26]. Moreover, both cranberry powder and PAC-rich extract have been shown to inhibit the adherence of *E coli* to vaginal epithelial cells in a dose-dependent manner [32]. Such an effect may be relevant to the prevention of UTIs, since in vitro bacteria adherence is significantly higher in vaginal epithelial cells from women with recurrent UTIs compared to controls [33]. Certainly, clinical studies are strongly recommended in order to confirm such a hypothesis.

Another potential mechanism of cranberry action against uropathogenic *E coli* is the non-enzymatic generation of nitric oxide (NO) by dismutation of nitrite to NO and NO_2 under mildly acidic conditions (Fig. 2) [34]. NO possesses potent antimicrobial activities that are both time- and concentration-dependent. In UTI, acidified nitrite may be a physiologically relevant source of NO produced by bacterial nitrate reductase activity and/or the local induction of inflammation-driven NO synthase activity [35].

Part of the recognized clinical benefit of cranberries in the management of UTIs is correlated to a significant relief of symptoms, which are mainly attributed to the inflammatory reaction triggered by pathogens invasion. Recently, it was demonstrated that these "symptom relief" effects of cranberry in UTIs could be attributed to anti-inflammatory actions of some of its ingredients. Specifically, in vitro studies suggested that UA, a main compound in cranberries inhibited the activity of cyclooxygenase-2, which represents a key molecule in many inflammatory pathways [36]. Moreover, cranberry extracts were shown to inhibit nuclear factor κB transcriptional activation in human T lymphocytes and significantly suppressed the release of interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor-α (TNF-α) from *E coli* lipopolysaccharide-stimulated human peripheral blood mononuclear cells, at a concentration of 50 μg/mL. Taken together, the above data suggests that cranberries probably attenuate part of the downstream signal transduction pathways that are triggered by bacterial-lipopolysaccharide, which in turn may lead to an excessive inflammatory reaction [36]. In addition, it was shown that anthocyanins and hydroxycinnamic acids isolated from cranberries reduced inflammation responses in human microvascular endothelial cells challenged with TNF-α by limiting up-regulation of cytokines and adhesion molecules [37].

In this aspect, several isolated cranberry phytochemicals, including flavonols, salicylic acid, resveratrol, and triterpenoids

were shown to exert anti-inflammatory actions in animal models [7,38]. Quercitrin, one of the cranberry's more abundant flavonols, reduced, in vivo, an index based on physiological observations (body weight, presence of blood in feces, and stool consistency) and ex vivo cytokine production in a rat model of colitis [39]. Also in rats, resveratrol inhibited inflammatory COX activity both before and after induction by N-nitrosodiethylamine [40]. Since UTIs are characterized by a number of inflammatory symptoms, it could be suggested that in addition to its anti-adhesive activities, cranberries may reduce the symptoms of UTI through anti-inflammatory mechanisms (Fig. 2). Notably, cranberries were also shown to be a powerful in vitro and in vivo source of antioxidants. Given that reducing oxidative stress may have immunomodulation properties that enhance the body's immune system and could potentially contribute to a better immune response in the case of UTIs (Fig. 2) [41]. However, such a hypothesis has not been verified in a clinical setting as of publication of this review.

Collectively, cranberry products appear to not inhibit bacterial growth and not sterilize the urinary tract. However, they may prevent bacterial adherence to uroepithelial cells thus reducing the development of UTI, and they could also reduce UTI related symptoms by suppressing inflammatory cascades as an immunologic response to bacteria invasion.

4. Clinical trials

The first clinical, although uncontrolled, study regarding the efficiency of cranberries in treating UTIs was published by Papas et al in 1966 [42]. These authors reported that 38 (63%) of 60 patients with bacteriuria and lower urinary tract symptoms who received 480 mL of cranberry juice daily for 3 weeks had evidence of persistent bacteriuria and 4 (7%) of them had no bacterial growth. With regard to the symptoms, 32 (53%) patients improved, but 6 weeks after the end of the treatment, bacteriuria reappeared in most of them [42]. Since the study of Pappas et al, several clinical trials evaluating whether or not cranberry products may prevent UTIs have been performed. These studies evaluated various patient populations, including sexually active adult women, elderly patients, children, and patients suffering from different medical conditions. In some of these studies, the primary parameter tested was UTI, while bacteriuria was the primary end point in other studies.

4.1. *Sexually active women with previous UTI*

A Finnish study by Kontiokari et al that received enormous interest by the media and expanded the use of cranberries in Europe, reported a significant reduction of the first recurrence of UTI in young women who received a cranberry-lingoberry concentrate for prophylaxis [43]. This randomized controlled trial included 150 women with a history of UTI caused by *E coli*. Subjects were randomized to either drink 50 mL/d of a juice concentrate mix containing lingoberry and European cranberry for 6 months, 100 mL of a probiotic *Lactobacillus* drink 5 days per week for 12 months, or they received no intervention. After 6 months of treatment, 16% of the lingoberry-cranberry group, 39% of the *Lactobacillus* group, and 36% of the control group had experienced one recurrence of an UTI. Thus, the absolute risk for UTI was reduced by 20%. Most interestingly, the authors observed that although the cranberry group stopped the treatment after 6 months, the infection rate remained lower in that group compared to the other groups [43].

The prophylactic value of cranberry juice (250 mL 3 times daily) or cranberry extract in tablets (twice daily) for 1 year was also evaluated in a Canadian study conducted by Stothers et al (Table 1) [44]. In this study, a total of 150 sexually active women with a history of a previous UTI received either placebo juice and placebo tablets, placebo juice and cranberry tablets, or cranberry juice and placebo tablets. The patients were followed for 1 year and the results showed that 32% of the placebo group experienced 1 symptomatic UTI during the year, compared with 20% in the cranberry juice group and 18% in the cranberry tablets group. The absolute risk reduction for UTI by cranberry products was 12% to 14% [44]. Another study by Stapleton et al was focused on the time to UTI and the rates of asymptomatic bacteriuria and urinary P-fimbriated *E coli* during a 6-month period in women who ingested either cranberry or placebo juice daily [45]. This study examined 176 premenopausal women with a history of recent UTI that were randomized to 1 of 3 arms: 4 and 8 oz of cranberry juice daily or placebo juice and followed up for a median of 168 days. The cumulative rate of UTI was 0.29 in the cranberry juice group and 0.37 in the placebo group ($P = .82$), while the adjusted hazard ratio for UTI was 0.68 (95% confidence interval, 0.33-1.39; $P = .29$). The proportion of women with P-fimbriated urinary *E coli* isolates during the intervention phase was 43.5% in the cranberry juice group and 80.0% in the placebo group. No difference concerning the mean dose adherence was noted. Minor adverse effects were also reported by 24.2% of those in the cranberry juice group and 12.5% in the placebo group. Collectively, this study showed that cranberry juice did not significantly reduce UTI risk compared with placebo. Thus, it was speculated that although the potential observed protective cranberry effects were consistent with previous studies, larger and well-powered studies of women with recurrent UTI are recommended [45].

An encouraging study for the protective effects of cranberry ingestion on asymptomatic bacteriuria and UTIs during pregnancy was conducted by Wing et al [46]. In this study, 188 women were randomized to receive either cranberry juice with each meal, cranberry juice at breakfast followed by placebo at lunch and dinner, or placebo at each meal. Notably, this study showed that there was a trend toward fewer UTIs both asymptomatic and symptomatic in the women that received multiple daily doses of cranberry juice compared to the placebo group. This trend also persisted in the group who received single doses of cranberry juice, although the magnitude of the difference was less [46]. This study, however, presented certain limitations that include the small sample size (due to withdrawal because of lack of tolerability) and the lack of bioassay for compliance. As a result, the study is underpowered, and its conclusions cannot easily be adopted.

Another randomized double-blind, placebo-controlled study by Barbarosa-Cesnik et al showed that cranberry juice failed to prevent recurrent urinary tract infections [47]. This study investigated the effects of cranberry juice on the risk of recurring UTI among 319 college women with an acute UTI.

Table 1 – Clinical trials evaluating the effect of cranberry consumption on sexually active women with previous UTI

Method, population	Intervention	Outcome	Ref.
Open R/150 women with previous UTI	50 mL of cranberry-lingoberry concentrate for 6 months or 100 mL of lactobacillus drink 5 days per week for 12 months or no intervention	Significant reduction in UTI: 16% for cranberry vs 39% for lactobacillus and 36% for no intervention	[43]
R, placebo, double-blind/150 women with previous UTI	3 groups: placebo juice + placebo tablets vs placebo juice + cranberry tablets vs cranberry juice + placebo tablets (Tablets were taken twice daily and juice 250 mL 3 times daily) for 1 year trial	Significant reduction in UTI both for cranberry juice (20%) and tablets (18%) compared with placebo (32%).	[44]
R, placebo-controlled/176 premenopausal women followed up for a median of 168 days with a history of recent UTI	4 oz and 8 oz of cranberry or placebo juice daily for 6 months	Cranberry juice did not significantly reduce UTI risk compared with placebo. Concurrent reduction in urinary P-fimbriated *E.coli* strains	[45]
R, placebo-controlled, double-blind/188 pregnant women at less than 16 weeks	240 mL cranberry juice 3 times daily or cranberry at breakfast and placebo at lunch and dinner or placebo 3 times daily for 6 weeks	Underpowered study. The group that received multiple daily doses of cranberry juice showed a trend toward fewer UTIs	[46]
R, double-blind placebo-controlled study/319 college women with an acute UTI	8 oz cranberry juice twice daily for 6 months or until a second UTI	Women cranberry juice did not experience a decrease in the 6-month incidence of a second UTI compared with those drinking a placebo	[47]
R, double-blind study/137 women with 2 or more antibiotic-treated UTIs in the last 12 months	500 mg of cranberry extract or 100 mg of TMP for 6 months	TMP had a limited advantage over cranberry extract in the prevention of recurrent UTIs. TMP had more adverse effects.	[48]
R, double-blind, double-dummy noninferiority study/221 premenopausal women with recurrent UTIs over 12 months	Cranberry capsules, 500 mg twice daily or TMP-SMX, 480 mg once daily for 12 months	TMP-SMX was more effective than cranberry capsules to prevent recurrent UTIs at the expense of emerging antibiotic resistance	[49]
R double-blind, cross-over/19 women with recurrent UTI (10 finished the study)	Cranberry capsule with 400 mg of cranberry solids or placebo for 3 months	Cranberry prevented UTI. 15 episodes of UTI in the placebo and 6 in the cranberry group.	[50]
Dose-escalation, single-blind study/28 women with 2 or more episodes of UTIs in the last 6 months	Oral administration of cranberry liquid blend agent at 15, 30, 45, 60 and 75 mL daily for 12 weeks	91% of the subjects remained free of recurrent UTIs for 3 months when taking a dose of = 60 mL/d	[51]

R, randomized; NR, non-randomized; SMX, sulfamethoxazole.

Participants were followed up until a second UTI or for 6 months, whichever came first. UTI was determined on the basis of the combination of symptoms and a urine culture positive for a known uropathogen. The study documented a 2-fold difference between treated and placebo groups, assuming in unblinded trials that 30% of participants would experience a UTI during the follow-up period. However, the actual observed rate in the placebo arm was only 14%. The study supported that among otherwise healthy college women with an acute UTI, those drinking 8 oz of 27% cranberry juice twice daily did not experience a decrease in the 6-month incidence of a second UTI, compared with those drinking a placebo [47]. However, interpretation of the aforementioned results may be confounded by the unexpectedly low rate of UTI recurrence after the 6-month intervention period. The authors also speculated that the placebo may contain an active component that may prevent UTIs. Moreover, the compliance of the study was based on self-reporting from the participants regarding consumption of the products. In this aspect, a reliable approach to ensuring compliance should be recommended to monitor the production of a cranberry metabolite in the urine in order to avoid inconclusive results.

The increasing prevalence of uropathogens resistant to antimicrobial agents has stimulated interest in cranberries to prevent recurrent UTIs. In this aspect, McMurdo et al conducted the first head-to-head double-blind comparison of the cranberry extract versus antibiotic prophylaxis (low-dose trimethoprim [TMP]) for the prevention of recurrent UTIs (Table 1) [48]. One hundred thirty-seven women aged >45 years with 2 or more antibiotic-treated UTIs in the previous 12 months were randomized to receive either 500 mg of cranberry extract or 100 mg of TMP for 6 months. The authors reported that TMP had an advantage over cranberry extract in the prevention of recurrent UTIs in older women, but TMP also had more adverse effects [48].

More recently, a double-blind, double-dummy non-inferiority clinical trial by Beerepoort et al was conducted on 221 premenopausal women with recurrent UTIs that were randomized to 12-month usage of either 480 mg/1x daily of the prophylaxis TMP-sulfamethoxazole (TMP-SMX), or 500 mg twice daily of cranberry capsules [49]. After 12 months, the mean number and the proportion of patients with at least 1 symptomatic UTI was significantly higher in the cranberry group compared to the TMP-SMX group. Median time to the first symptomatic UTI was 4 months for the cranberry and 8 months for the TMP-SMX group. After 1 month, in the cranberry group, 23.7% of fecal and 28.1% of asymptomatic bacteriuria *E coli* isolates were TMP-SMX resistant, whereas in the TMP-SMX group, 86.3% of fecal and 90.5% of asymptomatic bacteriuria *E coli* isolates were TMP-SMX resistant. Moreover, increased resistance rates for TMP, amoxicillin, and ciprofloxacin in *E coli* isolates after 1 month in the TMP-SMX group were

noted. After discontinuation of TMP-SMX, resistance reached baseline levels after 3 months. Antibiotic resistance did not increase in the cranberry group, while cranberries and TMP-SMX were equally well tolerated. The authors suggested that 480 mg once daily of TMP-SMX was more effective than 500 mg twice daily of cranberry capsules in preventing recurrent UTIs in premenopausal women, at the expense of emerging antibiotic resistance [49].

In a smaller double-blind crossover study by Walker et al (Table 1), 19 women with recurrent UTI received either a cranberry capsule or a placebo capsule for a 3-month period [50]. Then for the next 3 months, patients switched to the alternative treatment. The results favored the cranberry use, but this notion was extracted from only 10 patients who managed to finish the entire course of treatment. Of 21 episodes of UTI, 6 occurred in the cranberry group and 15 in the placebo group [50]. Another epidemiological, retrospective study that evaluated the relationship between sexual behavior and first time UTI in sexually active women reported that regular consumption of cranberry juice was associated with a decreased risk of contracting a UTI [52]. Despite the fact that this study was retrospective and examined first time UTIs, it contributed to the opinion that sexually active women could represent a population that may benefit from cranberry consumption.

Recently, Efros et al conducted a study in pre- and postmenopausal women who had recurrent UTIs, in order to determine the safety, tolerability and efficacy of a concentrated cranberry liquid blend, UTI-STAT with Proantinox (Table 1) [51]. To be eligible, women had to have experienced 2 or more episodes of UTIs in the previous 6 months before study entry. A total of 28 subjects were included in the study. The agent was orally administrated at 15, 30, 45, 60, and 75 mL daily for 12 weeks, and the primary end points were the safety, tolerability, and maximal tolerated dose. The secondary endpoints demonstrated that only 2 (9.1%) of 23 reported a recurrent UTI. At 12 weeks, a significant reduction in concern regarding recurrent UTIs and a significant increase in quality of life with regard to the physical functioning domain and role limitations from the physical health domain, as measured by the Medical Outcomes Study, short-form, 36-item questionnaire were noted [51]. However, this data did not provide conclusive evidence about the ability of UTI-STAT with Proantinox product to reduce recurrent UTI. Moreover, UTI recurrence is typically measured over a 6-month period, so the time interval of the study (3 months) was not long enough for recurrence to occur in participants.

4.2. *Elderly patients*

The first major clinical study on cranberry juice as a prophylactic measure for UTI was performed by Avorn et al in an elderly female population (average age 78 years) [22]. This large randomized double-blind study included 153 asymptomatic elderly women who received either 300 mL daily of cranberry juice cocktail or a placebo beverage. The study examined the effects on the primary outcomes of bacteriuria (>10^8/L) and pyuria (Table 2). Infected urine sample were reduced in the cranberry group by 42% compared to the control group, while there was less need for antibiotic use. However, the interpretation of the findings is weakened because a precise definition exists only for bacteriuria and not for pyuria, while bacteriuria without pyuria is a common finding in elderly women that requires no treatment. The results of this study have also been questioned due to an imperfection in the baseline randomization. In particular, substantially more patients of the placebo group (25%) than those of the cranberry group (7%) had experienced a symptomatic UTI 6 months prior to the study. Only 18% to 21% of the patients at the baseline had documented bacteriuria or pyuria. Thus, this study did not show that cranberries reduced the incidence of symptomatic UTI, but it indicated a possible role of cranberries for treatment if the combination of bacteriuria and pyuria was thought to constitute an infection [22].

Another randomized, placebo-controlled, double-blind trial assessed whether cranberry juice ingestion was effective in reducing UTIs in older people in the hospital [53]. A total of 376 patients were randomized to receive either 300 mL of a commercial cranberry juice daily or a placebo beverage. Symptomatic UTI occurred in only 5.6% of the participants, and there was no difference between groups. However, there was a reduction in the cranberry group regarding the *E coli* infections. Despite having the largest sample size of any clinical trial assessing the effect of cranberry juice ingestion, the actual infection rate observed was lower than anticipated, making the study underpowered. The results of the study seem inconclusive due to the rather short intervention and observation period (18 and 35 days, respectively) [53]. Moreover, no precise conclusions can be drawn from this study because the placebo group did not get sufficient infections to make comparisons to the cranberry group statistically valid.

Two more studies involving cranberries and elderly patients have been conducted, but both were not randomized. Kirchhoff et al compared the incidence of UTI in 2 geriatric departments [54]. Patients were provided cranberry juice in one department and simple berry juice in the other. They observed no difference regarding the incidence of UTI in both groups [54]. The other study included 538 nursing home residents that received daily either 220 mL of cranberry juice or 6 capsules containing cranberry extract. Compared with historical controls, both groups presented a significant reduction in the incidence of UTI from 27 cases per month to 20 cases per month (Table 2) [55].

A more recent randomized, placebo-controlled, double-blind study was conducted on outpatients aged 20 to 79 years who were divided into a group that received daily either one bottle (125mL) of cranberry juice or a placebo beverage for 24 weeks [56]. The primary endpoint was relapse of UTI. In the subgroup analysis, relapse of UTI was observed in 16 (29.1%) of 55 patients who received cranberry juice and 31 (49.2%) of 63 patients who received a placebo beverage. Thus, it was speculated that cranberry juice prevented the recurrence of UTI in a limited female population aged 50 years or more who had a 24-week intake of the beverage [56]. Moreover, in a small randomized study, Haverkorn et al evaluated the use of cranberries by elderly patients with the use of a non-blinded cross-over design (Table 2) [57]. Elderly men and women (average age 81 years old) received either 15 mL of cranberry juice mixed with water or only water twice daily. After 4 weeks, the regimens were reversed. Only 17 patients managed

Table 2 – Clinical trials evaluating the effects of cranberry consumption on elderly patients

Method, population	Intervention	Outcome	Ref.
R, placebo-controlled, double-blind, no-intent to treat/153 elderly women	Daily consumption of 300 mL standard cranberry beverage or placebo drink for 6 months	Bacteriuria and pyuria were significantly reduced: 25% for the placebo vs 15% for the cranberry group	[22]
R, placebo-controlled, double-blind trial/376 elderly patients without previous history of UTI	Daily consumption of 300 mL cranberry juice or matching placebo beverage for a mean period of 18 days	No difference between groups regarding the UTI occurrence. Infections with *E coli* were significantly reduced in the cranberry group	[53]
NR, controlled/338 elderly patients in 2 geriatric units with mean stay of 4 weeks	Cranberry juice or usual mixed berry juice	No effect on UTI	[54]
NR, historical controls/538 nursing home elderly residents	220 mL of cranberry juice or 6 capsules with cranberry extract per day	Incidence of UTI was significantly reduced compared with historical controls	[55]
R, placebo-controlled, double blind in 118 outpatients aged 20 to 79 years	1 bottle (125 mL) of cranberry juice or the placebo beverage once daily, before going to sleep, for 24 weeks	Cranberry juice prevented the recurrence of UTI in a limited female population with 24-week intake of the beverage	[56]
R cross-over/38 elderly men and women (17 finished the study)	15 mL of cranberry juice vs water for 4 weeks	7 of 17 patients had reduction of bacteriuria during cranberry period	[57]

R, randomized; NR, non-randomized.

to complete the 4-week period, and data from only 7 patients were finally analyzed. There were fewer instances of bacteriuria during the cranberry period compared to the control period, thus providing supportive evidence for a possible preventive role for cranberry juice [57].

Collectively, the main drawback concerning the studies conducted on the elderly people deals with the uncertainty of whether some of these patients had a pre-existing infection, albeit they were asymptomatic. In all these studies involving geriatrics, pre-enrollment data on bacteriuria/pyuria are absent. Furthermore, a significant proportion of these patients could have an asymptomatic bacteriuria/pyuria on an ongoing basis.

4.3. *Pediatric patients*

The effect of cranberries in pediatric patients with medical conditions predisposing to UTIs has recently been evaluated. A randomized double-blind, placebo-controlled clinical trial evaluating the effect of cranberry juice on nasopharyngeal and colonic bacterial flora with a total of 341 children receiving either 300 mL cranberry juice (n = 171) or a placebo (n = 170) for 3 months was performed in day care centers [58]. This study showed that cranberry juice was well accepted by the children, but led to no change in either the bacterial flora in the nasopharynx or the bacterial fatty acid composition of stools. Thus, it was speculated that although cranberry consumption seems to have beneficial effects on urinary health, this is not compromised by other unexpected antimicrobial effects [58].

More recently, a randomized, double-blind, placebo-controlled trial with a total of 263 children treated for UTI was performed throughout 7 hospitals in Finland [59]. Patients treated for UTI were randomized to receive either cranberry juice or placebo for a period of 6 months. The children were followed-up for 1 year for recurrent UTIs. Twenty children (16%) in the cranberry group and 28 (22%) in the placebo group had at least 1 recurrent UTI, a difference which did not reach statistical significance. Similarly the total number of UTI episodes was 27 and 47 in the cranberry and placebo groups, respectively, which also did not reach statistical significance [59]. In this study, 45% of the participants were toddlers and only 30% had more than 2 UTIs at baseline. Interestingly, although this study did not demonstrate a significant difference in the proportion of children who had at least 1 UTI after enrollment, when the incidence density (UTIs per person per year) was compared the treatment group, it showed a 45% lower incidence density [59]. Another study featured a small randomized placebo-controlled study that was powered to detect a 30% decrease in the rate of symptomatic UTIs conducted on 40 children receiving cranberry juice with high PACs concentrations or cranberry juice with no PACs for a 1-year period [60]. This study included toilet trained children up to 18 years of age that had experienced at least 2 UTIs in the calendar year prior enrollment. Children receiving cranberry juice with high PAC concentrations showed a 65% reduction in the risk of UTIs [60].

Schlager et al conducted a crossover, placebo-controlled, double-blind study in 15 children with a neurogenic bladder who received intermittent catheterization [61]. The children received either 300mL of a cranberry concentrate or a placebo beverage each for a 3-month period. However, no benefit from cranberry use was observed [61]. In fact, the frequency of bacteriuria was 75% during both periods and the number of UTIs was not significantly different [61]. In this context, it should be noted that this study was underpowered with only 15 participants. In addition, it was only conducted for 3 months which is not long enough to observe an effect from the cranberry on the bacteria. In a randomized, single-blind, crossover study by Foda et al, a cranberry cocktail (15 mL/kg per day) or water was provided to 40 children each for 6 months [62]. However, only 21 patients managed to finish the study and no difference was noticed regarding UTI incidence in both groups [62]. Thus, this study was underpowered with a 50% drop out rate, and its results seem inconclusive concerning the efficiency of cranberry in preventing UTIs in the pediatric neuropathic bladder population.

There was also a small uncontrolled, observational study conducted by Rogers et al that investigated the efficiency of cranberry for the treatment of UTIs [63]. In this study, 7

children with neuropathic bladder and *E coli* at the onset received 2 glasses of cranberry juice per day. Although a quantitative decline in pyuria occurred, urine cultures continued to be positive for *E coli*. This study, however, was also quoted because a high frequency of pre-existing becteriuria could be anticipated, therefore making it difficult to differentiate between no infection and low grade asymptomatic infection (Table 3) [63].

4.4. *Adult patients with medical conditions predisposing to UTIs*

Cranberries have also been studied in adult patients with neuropathic bladder that had a preceding spinal cord injury. A double-blind, randomized, placebo-controlled trial with 6 months of follow-up was conducted by Lee et al in 305 spinal cord injury patients with neurogenic bladder [64]. Twice daily, patients received either 1 g of methenamine hippurate or 800 mg of cranberry extract; however, the study did not confirm a benefit from daily cranberry consumption [64]. Equivalent to the above study, a randomized double-blind study was conducted by Waites et al [65]. In this study, 48 patients with a spinal cord injury and neurogenic bladder received either 2 g of concentrated cranberry juice or a placebo for a 6-month period. No differences or trends though were detected between groups with respect to bacterial counts and types or episodes of symptomatic UTIs (Table 3) [65].

Another randomized double-blind placebo-controlled trial was conducted by Cowan et al to determine the effect of cranberry on UTIs in patients undergoing radiotherapy for cancer of the bladder or cervix [66]. Participants were randomized to receive either cranberry juice twice daily for the duration of radiotherapy and for 2 weeks following treatment or a placebo beverage for the same duration. The study reported no difference regarding the incidence of UTIs between the 2 groups. Still, the compliant population was small (n = 32), and this undermined the power of the study to reliably evaluate the effect of cranberry juice on urinary symptoms [66]. However, a limitation of this study was the use of cranberry juice as a nonstandardized preparation, so it is unclear whether the dosage of proanthocyanidin was actually administered. Moreover, the study reported reduced compliance observed in the treatment group, due to poor palatability of the cranberry juice. No significant differences were found in a study by Campbell et al that compared the effect of cranberry juice and apple juice on the management of urinary symptoms in patients with prostate cancer who were undergoing external beam radiotherapy [66]. However, in this study, the endpoint did not include the incidence of urinary infections as only urinary symptoms were considered, and the 120 patients enrolled were randomly sorted into 2 equivalent groups treated with either cranberry juice or apple juice.

A more recent non-randomized study conducted on 370 prostate cancer patients investigated the preventive effect of an enteric-coated, highly standardized cranberry extract on the risk of lower UTIs and urinary symptoms during radiotherapy [67]. Compliance was excellent, with no adverse effects or allergic reactions being observed. In the cranberry cohort (n = 184), 16 lower UTIs (8.7%) were observed; whereas in the control group (n = 186), 45 lower UTIs (24.2%) were recorded at a statistically significant level. Moreover, lower rates of nocturia, urgency, micturition frequency, and dysuria were observed in the cranberry group [67]. This study suffered from lack of randomization, but it applied enteric coating of cranberry extract to prevent possible degradation of proanthocyanidines during processing, potential instability in gastric juices, and possible interaction with gastric *Helicobacter pylori*. Accordingly, a clinical trial of Vidlar et al, conducted on 42 men at risk for prostate disease with lower urinary tract symptoms, elevated PSA (with negative prostate biopsy), and clinically confirmed chronic prostatitis, documented that cranberries may ameliorate lower urinary tract symptoms, independent of benign prostatic hyperplasia or C-reactive protein level (Table 4) [69]. Moreover, in a pilot study

Table 3 – Clinical trials evaluating cranberry consumption in pediatric patients

Method, population	Intervention	Outcome	Ref.
R, double-blind placebo-controlled study/341 children treated for UTI in daily care centers	300 mL cranberry juice or a placebo for 3 months	Cranberry juice was well accepted. Cranberry juice did not affect bacterial flora in the nasopharynx and bacterial fatty acid composition of stools.	[58]
R, double-blind placebo-controlled trial/263 children treated for UTI followed-up for 1 year	Cranberry juice or placebo for 6 months	16% and 22% of children in cranberry and placebo groups had at least 1 recurrent UTI. 27 and 47 total number of UTI episodes in the cranberry and placebo groups.	[59]
R, placebo controlled trial/40 toilet trained children with a history of 2 UTIs	2 mL/kg cranberry juice containing 37% PAC or cranberry juice with no PAC for 1 year	A 65% reduction in the risk of UTIs	[60]
R, double-blind, cross-over trial/15 children with neurogenic bladder	300 mL cranberry concentrate or placebo for 3 months	No benefits in preventing UTI	[61]
R, single-blind, cross-over trial/40 children with neurogenic bladder (21 finished the study)	15 mL/kg per day cranberry cocktail or water for 6 months	No benefit in preventing UTI or bacteriuria	[62]
Pilot open cross-over study/7 children with neuropathic bladder and E.coli	Two glasses of cranberry juice per day	A quantitative decline in pyuria but the bacterium did not clear.	[63]

R, randomized; NR, non-randomized.

by Reid et al, in 15 spinal cord injury patients (mean age 42 years), cranberries were reported to reduce the bacterial biofilm load in the bladder, as well as the adhesion of Gram-negative and -positive bacteria to cells [70]. Conversely, water intake had no effect on bacterial adhesion or biofilm presence [70].

A recent retrospective study by Pagonas et al was performed to assess the prophylaxis of cranberry, L-methionine, and their combination against recurrent UTIs in 39, 25, and 18 renal transplant outpatients [71]. In this study, 30 patients without prophylaxis served as controls. The mean duration of prophylaxis was 22.1±18.7 months. Prophylaxis using cranberry and/or methionine led to an overall reduction in the incidence of recurrent UTIs in the renal transplant population by about 50%, whereas there was no change in a control group not receiving prophylaxis. Interestingly, besides the reduced incidence of UTI episodes, cranberry and L-methionine decreased the number of symptomatic or pyuric patients [71]. However, this study was limited by its retrospective character; and therefore, a prospective, randomized, controlled study will be necessary for more precise conclusions to be drawn.

4.5. *Meta-analysis of clinical data*

Jepson et al have systematically reviewed the evidence regarding cranberry use in UTI prevention [72,73]. This meta-analysis was conducted on 10 studies that included 1049 patients (5 crossover and 5 parallel groups). Cranberry/cranberry-lingonberry juice versus placebo or water were evaluated in 7 studies, cranberry tablets versus placebo tablets in 4 studies, and both juice and tablets in one study. Cranberry products significantly reduced the incidence of UTIs at 12 months compared with placebo/control. Moreover, cranberry products were more effective in reducing the incidence of UTIs in women with recurrent UTIs. The authors concluded that the existing evidence suggested that cranberry juice should be recommended for the prevention of UTIs in women with symptomatic UTIs, but the data were discouraging for its effectiveness in older populations, as well as in patients with a neuropathic bladder. Furthermore, it was speculated that there was no clear evidence regarding the appropriate dose and treatment duration for the intervention to be most effective [72,73].

A more recent updated review included a total of 24 studies (6 cross-over studies; 11 parallel group studies with 2 arms; 5 with 3 arms; and 2 studies with a factorial design) with a total of 4473 participants [74]. Data included in the meta-analyses showed that, compared with placebo, water, or non-treatment, cranberry products were less effective than previously indicated in reducing the occurrence of symptomatic UTI overall or for any of the reviewed subgroups: women with recurrent UTIs, older people, pregnant women, children with

Table 4 – Clinical trials evaluating cranberry consumption on adult patients with medical conditions predisposing to UTIs, such as spinal cord injury, neurogenic bladder, prostate cancer or hyperplasia

Method, population	Intervention	Outcome	Ref.
R, double-blind placebo trial with 6 months follow-up/305 spinal cord injured patients with neurogenic bladder	Patients received either 1 g methanamine hippurate or 800 mg cranberry extract twice daily for 6 months	No-longer UTI-free periods compared to placebo were observed in both groups.	[64]
R, double-blind study/48 patients with spinal cord injury and neurogenic bladder	2 g of concentrated cranberry juice or placebo for 6 months	No differences or trends were detected between groups with respect to bacterial counts and types or episodes of symptomatic UTIs	[65]
R, placebo-controlled, double-blind designed/128 patients bladder or cervix cancer undergoing pelvic radiotherapy (32 patients)	Cranberry juice twice daily or a placebo beverage for the duration of radiotherapy and 2 weeks after treatment (6 weeks in total)	No difference regarding UTI incidence between groups	[66]
R, double-blind study/112 patients with prostate cancer undergoing external beam radiotherapy	354 mL cranberry juice or apple juice per day	No difference regarding UTI incidence	[68]
NR study/370 patients with prostate cancer undergoing external beam radiotherapy	Enteric-coated, highly standardized cranberry extract containing (200 mg cranberry extract titered as 30% PACs) for 6-7 weeks	Significant reduction of the risk of UTIs and urinary symptoms	[67]
R, double-blind study/42 men with LUTS, elevated PSA and/or benign prostatic hyperplasia	1500 mg of dried powdered cranberries or no cranberry treatment per day for 6 months	Statistically significant improvement in the IPSS, urination parameter & PSA level in the cranberry group	[69]
Pilot study with open cross-over design/15 spinal cord injured patients	Drinking 3 glasses of water or cranberry juice daily for 7 days	Cranberry juice reduced the biofilm load and the bacteria adhesion to the cells compared to the water intake	[70]
Retrospective study/82 renal transplant outpatients	2×50 mL/d cranberry juice or 500 mg/d L-methionine or a combination of both; mean duration 22.1±18.7 months	A 50% overall reduction in the incidence of recurrent UTIs using cranberry and/or L-methionine, cranberry and L-methionine decreased the number of symptomatic or pyuric patients	[71]

R, randomized; NR, non-randomized; LUTS, lower urinary tract symptoms; IPSS, International Prostate Symptom Score.

recurrent UTI, cancer patients, or people with neuropathic bladder or spinal injury. These data are not absolutely conclusive since many studies reported low compliance and high withdrawal/dropout problems. Moreover, most studies of other cranberry products (tablets and capsules) did not report how much of the 'active' ingredient the product contained, and therefore, the products may not have had enough potency to be effective. In this aspect, the authors suggested that other preparations (such as powders) need to be quantified using standardized methods to ensure the potency and quantity of the 'active' ingredient prior to being evaluated in clinical studies or recommended for use [74]. Thus, the currently available evidence appears to be of poor quality and does not support cranberry consumption for the reduction of UTIs.

5. Conclusions

Cranberry (*V macrocarpon*) has been used for decades to prevent UTIs, which are among the most common bacterial infections in women. Cranberries that contain important dietary flavonoids, including PACs, have been extensively studied in vitro, thus unfolding new perspectives as far as their preventive role in UTIs. Based on these promising results, ongoing clinical trials are being conducted on different subpopulations to determine the exact mechanisms of action, as well as the clinical benefits of cranberry consumption in the management of UTIs. The beneficial effects of cranberries against UTIs appear to be mainly ascribed to the prevention of bacterial adherence to uroepithelial cells that in turn may reduce the development of UTI. Moreover, cranberries are supposed to reduce UTI related symptoms by suppressing inflammatory cascades as an immunologic response to bacteria invasion. Currently available evidence indicates a possible benefit overall from the use of cranberries in UTIs. However, cranberry juice for the prevention of UTIs is currently recommended only in women with symptomatic UTIs. The existing data remain inconclusive regarding its effectiveness in other populations that are at increased risk for contracting UTIs, such as the elderly and neuropathic bladder patients, since there are design flaws and underpowered. It should be emphasized that the beneficial effects of cranberries against UTI seem to be exclusively prophylactic (aid in preventing the development of infection) but not therapeutic (inactive against existing UTIs). Furthermore, there is no clear evidence regarding the appropriate dose and treatment duration in order for the intervention to be most effective. There is also considerable controversy concerning which well-defined ingredients of cranberry products are actually responsible for the beneficial effects against UTIs. Up until now, the evidence from a number of studies suggested that PACs are the major compounds responsible for these beneficial effects. Poor bioavailability and potential metabolism of cranberry bioactive ingredients, including PACs, may be responsible for the low efficacy of cranberries in clinical trials. Thus, future studies investigating the absorption efficiency and bioavailability, as well as the potential metabolism of cranberry ingredients after consumption by humans or animals, are strongly recommended. Moreover, there is a lack of standardization of cranberry products used throughout the various clinical trials. Notably, cranberry products that were found in the market widely differed in their phenolic content and distribution, with some products completely devoid of flavan-3-ols and others containing highly purified ones, either in A-type PACs or in anthocyanins [75].

Taking into account the cost and the increasing antimicrobial resistance of antibiotic regimens, the possibility of cranberry products acting as non-antibiotic alternatives seems to be promising. However, the results of the reviewed studies should not be viewed as conclusive, since many of the previously presented clinical trials appear to suffer from severe limitations, including improper randomization, small populations, short trial durations, large drop-out rates, and lack of standardization of administrated cranberry products. Further properly designed studies that address all of the above mentioned issues are certainly justified in order to conclusively determine the effectiveness of cranberries in the prevention of UTIs in susceptible populations.

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REFERENCES

[1] Roberts AP, Phillips R. Bacteria causing symptomatic urinary tract infection or asymptomatic bacteriuria. J Clin Pathol 1979;32:492–6.
[2] Johnson JR, Kaster N, Kuskowski MA, Ling GV. Identification of urovirulence traits in *Escherichia coli* by comparison of urinary and rectal *E coli* isolates from dogs with urinary tract infection. J Clin Microbiol 2003;41:337–45.
[3] Gupta K. Emerging antibiotic resistance in urinary tract pathogens. Infect Dis Clin North Am 2003;17:243–59.
[4] Pedersen CB, Kyle J, Jenkinson AM, Gardner PT, McPhail DB, Duthie GG. Effects of blueberry and cranberry juice consumption on the plasma antioxidant capacity of healthy female volunteers. Eur J Clin Nutr 2000;54:405–8.
[5] Macheix JJ, Sapis JC, Fleuriet A. Phenolic compounds and polyphenoloxidase in relation to browning in grapes and wines. Crit Rev Food Sci Nutr 1991;30:441–86.
[6] Neto CC. Cranberry and its phytochemicals: a review of in vitro anticancer studies. J Nutr 2007;137:186S–93S.
[7] Pappas E, Schaich KM. Phytochemicals of cranberries and cranberry products: characterization, potential health effects, and processing stability. Crit Rev Food Sci Nutr 2009;49:741–81.
[8] Lin L-Z, Harnly JM. A screening method for the identification of glycosylated flavonoids and other phenolic compounds using a standard analytical approach for all materials. J Agric Food Chem 2007;55:1084–96.
[9] USDA database for the flavonoid content of selected foods. Nutrient Data Laboratory, Beltsville Human Nutrition Research Center, Agricultural Research Service, U.S. Department of Agriculture, 2011.

[10] USDA Database for the proanthocyanidin content of selected foods. Nutrient Data Laboratory, Beltsville Human Nutrition Research Center, Agricultural Research Service, U.S. Department of Agriculture, 2004.
[11] Howell AB, Reed JD, Krueger CG, Winterbottom R, Cunningham DG, Leahy M. A-type cranberry proanthocyanidins and uropathogenic bacterial anti-adhesion activity. Phytochemistry 2005;66:2281–91.
[12] Kondo M, MacKinnon SL, Craft CC, Matchett MD, Hurta RA, Neto CC. Ursolic acid and its esters: occurrence in cranberries and other *Vaccinium* fruit and effects on matrix metalloproteinase activity in DU145 prostate tumor cells. J Sci Food Agric 2011;91:789–96.
[13] He XL, Liu RH. Cranberry phytochemicals: isolation, structure elucidation, and their antiproliferative and antioxidant activities. J Agric Food Chem 2006;54:7069–74.
[14] Wu X, Beecher GR, Holden JM, Haytowitz DB, Gebhardt SE, Prior RL. Concentrations of anthocyanins in common foods in the United States and estimation of normal consumption. J Agric Food Chem 2006;54:4069–75.
[15] Raghavan SR, Richards MP. Partitioning and inhibition of lipid oxidation in mechanically separated turkey by components of cranberry press cake. J Agric Food Chem 2006;54:6403–8.
[16] Duke JA. Handbook of phytochemical constituents of GRAS herbs and other economic plants (and database) Boca Raton. Florida: CRC Press, Inc; 1992.
[17] Koponen JM, Happonen AM, Mattila PH, Törrönen AR. Contents of anthocyanins and ellagitannins in selected foods consumed in Finland. J Agric Food Chem 2007;55:1612–9.
[18] Rimando AM, Kalt W, Magee JB, Dewey J, d Ballington JR. Resveratrol, pterostilbene, and piceatannol in *Vaccinium* berries. J Agric Food Chem 2004;52:4713–9.
[19] Kinney AB, Blount M. Effect of cranberry juice on urinary pH. Nurs Res 1979;28:287–90.
[20] Jackson B, Hicks LE. Effect of cranberry juice on urinary pH in older adults. Home Healthc Nurse 1997;15:198–202.
[21] Bodel PT, Cotran R, Kass EH. Cranberry juice and the antibacterial action of hippuric acid. J Lab Clin Med 1959;54: 881–8.
[22] Avorn J, Monane M, Gurwitz JH, Glynn RJ, Choodnovskiy I, Lipsitz LA. Reduction of bacteriuria and pyuria after ingestion of cranberry juice. JAMA 1994;271:751–4.
[23] Lowe FC, Fagelman E. Cranberry juice and urinary tract infections: what is the evidence? Urology 2007;57:407–13.
[24] Sobota AE. Inhibition of bacterial adherence by cranberry juice: potential use for the treatment of urinary tract infections. J Urol 1984;131:1013–6.
[25] Di Martino P, Agniel R, David K, Templer C, Gaillard JL, et al. Reduction of *Escherichia coli* adherence to uroepithelial bladder cells after consumption of cranberry juice: a double-blind randomized placebo-controlled cross-over trial. World J Urol 2006;24:21–7.
[26] Raz R, Chazan B, Dan M. Cranberry juice and urinary tract infection. Clin Infect Dis 2004;38:1413–9.
[27] Zafriri D, Ofek I, Adar R, Pocino M, Sharon N. Inhibitory activity of cranberry juice on adherence of type 1 and type P fimbriated *Escherichia coli* to eucaryotic cells. Antimicrob Agents Chemother 1989;33:92–8.
[28] Ofek I, Goldhar J, Zafriri D, Lis H, Adar R, Sharon N. Anti-*Escherichia coli* adhesin activity of cranberry and blueberry juices. N Engl J Med 1991;324:1599.
[29] Howell AB, Vorsa N, Der Marderosian A, Foo LY. Inhibition of the adherence of P-fimbriated *Escherichia coli* to uroepithelial-cell surfaces by proanthocyanidin extracts from cranberries. N Engl J Med 1998;339:1085–6.
[30] Terris MK, Issa MM, Tacker JR. Dietary supplementation with cranberry concentrate tablets may increase the risk of nephrolithiasis. Urology 2001;57:26–9.
[31] Foo LY, Lu Y, Howell AB, Vorsa N. The structure of cranberry proanthocyanidins which inhibit adherence of uropathogenic P-fimbriated *Escherichia coli* in vitro. Phytochemistry 2000;54:173–81.
[32] Gupta K, Chou MY, Howell A, Wobbe C, Grady R, Stapleton AE. Cranberry products inhibit adherence of p-fimbriated *Escherichia coli* to primary cultured bladder and vaginal epithelial cells. J Urol 2007;177:2357–60.
[33] Nahata MC, Cummins BA, McLeod DC, Butler R. Predictability of methenamine efficacy based on type of urinary pathogen and pH. J Am Geriatr Soc 1981;29:236–9.
[34] MacMicking J, Xie QW, Nathan C. Nitric oxide and macrophage function. Annu Rev Immunol 1997;15:323–50.
[35] Rhee KY, Charles M. Antimicrobial mechanisms of cranberry juice. Clin Infect Dis 2004;39:877.
[36] Huang Y, Nikolic D, Pendland S, Doyle BJ, Locklear TD, Mahady GB. Effects of cranberry extracts and ursolic acid derivatives on P-fimbriated *Escherichia coli*, COX-2 activity, pro-inflammatory cytokine release and the NF-kappabeta transcriptional response in vitro. Pharm Biol 2009;47:18–25.
[37] Youdim KA, McDonald J, Kalt W, Joseph JA. Potential role of dietary flavonoids in reducing microvascular endothelium vulnerability to oxidative and inflammatory insults. J Nutr Biochem 2002;13:282–8.
[38] Cote J, Caillet S, Doyon G, Sylvain JF, Lacroix M. Bioactive compounds in cranberries and their biological properties. Crit Rev Food Sci Nutr 2010;50:666–79.
[39] Comalada M, Camuesco D, Sierra S, Ballester I, Xaus J, Galvez J, et al. In vivo quercitrin anti-inflammatory effect involves release of quercetin, which inhibits inflammation through down-regulation of the NF-κB pathway. Eur J Immunol 2005;35:584–92.
[40] Khanduja KL, Bhardwaj A, Kaushik G. Resveratrol inhibits N-nitrosodiethylamine-induced ornithine decarboxylase and cyclooxygenase in mice. J Nutr Sci Vitaminol 2004;50:61–5.
[41] Wahle KW, Brown I, Rotondo D, Heys SD. Plant phenolics in the prevention and treatment of cancer. Adv Exp Med Biol 2011;698:36–51.
[42] Papas PN, Brusch CA, Ceresia GC. Cranberry juice in the treatment of urinary tract infections. Southwest Med 1966;47: 17–20.
[43] Kontiokari T, Sundqvist K, Nuutinen M, Pokka T, Koskela M, Uhari M. Randomised trial of cranberry-lingonberry juice and *Lactobacillus* GG drink for the prevention of urinary tract infections in women. BMJ 2001;322:1571–3.
[44] Stothers L. A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. Can J Urol 2002;9:1558–62.
[45] Stapleton AE, Dziura J, Hooton TM, Cox ME, Yarova-Yarovaya Y, Chen S, et al. Recurrent urinary tract infection and urinary *Escherichia coli* in women ingesting cranberry juice daily: a randomized controlled trial. Mayo Clin Proc 2012;87:143–50.
[46] Wing DA, Rumney PJ, Preslicka CW, Chung JH. Daily cranberry juice for the prevention of asymptomatic bacteriuria in pregnancy: a randomized, controlled pilot study. J Urol 2008;180:1367–72.
[47] Barbosa-Cesnik C, Brown MB, Buxton M, Zhang L, DeBusscher J, Foxman B. Cranberry juice fails to prevent recurrent urinary tract infection: results from a randomized placebo-controlled trial. Clin Infect Dis 2011;52:23–30.
[48] McMurdo ME, Argo I, Phillips G, Daly F, Davey P. Cranberry or trimethoprim for the prevention of recurrent urinary tract infections? A randomized controlled trial in older women. J Antimicrob Chemother 2009;63:389–95.
[49] Beerepoot MA, ter Riet G, Nys S, van der Wal WM, de Borgie CA, de Reijke TM, et al. Cranberries vs antibiotics to prevent urinary tract infections: a randomized double-blind

noninferiority trial in premenopausal women. Arch Intern Med 2011;171:1270–8.
[50] Walker EB, Barney DP, Mickelsen JN, Walton RJ, Mickelsen RA. Cranberry concentrate: UTI prophylaxis. J Fam Pract 1997;45:167–8.
[51] Efros M, Bromberg W, Cossu L, Nakeleski E, Katz AE. Novel concentrated cranberry liquid blend, UTI-STAT with Proantinox, might help prevent recurrent urinary tract infections in women. Urology 2010;76:841–5.
[52] Foxman B, Geiger AM, Palin K, Gillespie B, Koopman JS. First-time urinary tract infection and sexual behavior. Epidemiology 1995;6:162–8.
[53] McMurdo ME, Bissett LY, Price RJ, Phillips G, Crombie IK. Does ingestion of cranberry juice reduce symptomatic urinary tract infections in older people in hospital? A double-blind, placebo-controlled trial. Age Ageing 2005;34:256–61.
[54] Kirchhoff M, Renneberg J, Damkjaer K, Pietersen I, Schroll M. Can ingestion of cranberry juice reduce the incidence of urinary tract infections in a department of geriatric medicine? Ugeskr Laeger 2001;163:2782–6.
[55] Dignam R, Ahmen M, Denman S. The effect of cranberry juice on UTI rate in a long-term care facility. J Am Geriatr Soc 1997;45:169.
[56] Takahashi S, Hamasuna R, Yasuda M, Arakawa S, Tanaka K, Ishikawa K, et al. A randomized clinical trial to evaluate the preventive effect of cranberry juice (UR65) for patients with recurrent urinary tract infection. J Infect Chemother 2013;19:112–7.
[57] Haverkorn MJ, Mandigers J. Reduction of bacteriuria and pyuria using cranberry juice. JAMA 1994;272:590.
[58] Kontiokari T, Salo J, Eerola E, Uhari M. Cranberry juice and bacterial colonization in children—a placebo-controlled randomized trial. Clin Nutr 2005;24:1065–72.
[59] Salo J, Uhari M, Helminen M, Korppi M, Nieminen T, Pokka T, et al. Cranberry juice for the prevention of recurrences of urinary tract infections in children: a randomized placebo-controlled trial. Clin Infect Dis 2012;54:340–6.
[60] Afshar K, Stothers L, Scott H, MacNeily AE. Cranberry juice for the prevention of pediatric urinary tract infection: a randomized controlled trial. J Urol 2012;188:1584–7.
[61] Schlager TA, Anderson S, Trudell J, Hendley JO. Effect of cranberry juice on bacteriuria in children with neurogenic bladder receiving intermittent catheterization. J Pediatr 1999;35:698–702.
[62] Foda MM, Middlebrook PF, Gatfield CT, Potvin G, Wells G, Schillinger JF. Efficacy of cranberry in prevention of urinary tract infection in a susceptible pediatric population. Can J Urol 1995;2:98–102.
[63] Rogers J. Pass the cranberry juice. Nurs Times 1991;87:36–7.
[64] Lee BB, Haran MJ, Hunt LM, Simpson JM, Marial O, Rutkowski SB, et al. Spinal-injured neuropathic bladder antisepsis (SINBA) trial. Spinal Cord 2007;45:542–50.
[65] Waites KB, Canupp KC, Armstrong S, DeVivo MJ. Effect of cranberry extract on bacteriuria and pyuria in persons with neurogenic bladder secondary to spinal cord injury. J Spinal Cord Med 2004;27:35–40.
[66] Cowan CC, Hutchison C, Cole T, Barry SJ, Paul J, Reed NS, et al. A randomised double-blind placebo-controlled trial to determine the effect of cranberry juice on decreasing the incidence of urinary symptoms and urinary tract infections in patients undergoing radiotherapy for cancer of the bladder or cervix. Clin Oncol (R Coll Radiol) 2012;24:e31–8.
[67] Bonetta A, Di Pierro F. Enteric-coated, highly standardized cranberry extract reduces risk of UTIs and urinary symptoms during radiotherapy for prostate carcinoma. Cancer Manag Res 2012;4:281–6.
[68] Campbell G, Pickles T, D'Yachkova Y. A randomised trial of cranberry versus apple juice in the management of urinary symptoms during external beam radiation therapy for prostate cancer. Clin Oncol (R Coll Radiol) 2003;15:322–8.
[69] Vidlar A, Vostalova J, Ulrichova J, Student V, Stejskal D, Reichenbach R, et al. The effectiveness of dried cranberries (*Vaccinium macrocarpon*) in men with lower urinary tract symptoms. Br J Nutr 2010;104:1181–9.
[70] Reid G, Hsiehl J, Potter P, Mighton J, Lam D, Warren D, et al. Cranberry juice consumption may reduce biofilms on uroepithelial cells: pilot study in spinal cord injured patients. Spinal Cord 2001;39:26–30.
[71] Pagonas N, Hörstrup J, Schmidt D, Benz P, Schindler R, Reinke P, et al. Prophylaxis of recurrent urinary tract infection after renal transplantation by cranberry juice and L-methionine. Transplant Proc 2012;44:3017–21.
[72] Jepson RG, Craig JC. A systematic review of the evidence for cranberries and blueberries in UTI prevention. Mol Nutr Food Res 2007;51:738–45.
[73] Jepson RG, Craig JC. Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev 2008;1:CD001321.
[74] Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev 2012;10:CD001321.
[75] Sánchez-Patán F, Bartolomé B, Martín-Alvarez PJ, Anderson M, Howell A, Monagas M. Comprehensive assessment of the quality of commercial cranberry products. Phenolic characterization and in vitro bioactivity. J Agric Food Chem 2012;60:3396–408.