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REVIEW

Cranberry products in the prevention of urinary tract infections: examining the evidence

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Abstract: Cranberry (*Vaccinium macrocarpon*) juice and extracts are widely used and recommended as folk remedy for prophylaxis of urinary tract infections (UTIs). Its putative mechanism is an anti-adhesive effect that prevents docking of bacteria on host tissues. The anti-adhesion quality is attributed to A-type proanthocyanidins (PACs), a group of polyphenols that has a restricted occurrence in cranberries and a few related plants. Clinical trials with cranberry have provided a mixed evidence on behalf of UTI prophylaxis. In some trials, a benefit could not be detected due to lower than calculated UTI recurrence rates, in others failure had retrospectively been blamed on underdosing of cranberry products. To circumvent such problems, cranberry products need to be standardized for the bioactive principle of PAC and administered at a sufficient dose. Further characterization of PAC bioavailability, improvement of the currently inconvenient prescriptions, and above all of the palatability for patients is strongly recommended. Larger staged trials should then be carried out in patients with relevant UTI risks.

Keywords: cranberry (*Vaccinium macrocarpon* Aiton), urinary tract infection, proanthocyanidins, anti-adhesion, p-fimbriae

Introduction

Dried fruits, juice, or extracts of the American cranberry (*Vaccinium macrocarpon*) have become increasingly popular in patients with recurrent urinary tract infections (UTIs). Physicians have adopted the folk remedy from the American Indians, and its presumed benefit has been scientifically explored since the 1950s.

Laboratory research has suggested the interference of cranberry products with the adhesion of bacteria to host tissue, eg, the bladder mucosa, as a unique and hitherto unknown anti-infective mechanism. After some landmark clinical trials had shown cranberry juice or extracts to be effective for prophylaxis of UTI, subsequent trials with negative outcomes had rendered the current evidence debatable.

Anti-adhesion effects as putative anti-infective mechanism

Cranberry juice had at first been assumed to halt bacterial growth by acidifying the urine[1–3] or to harbor bactericidal/bacteriostatic compounds,[4,5] but studies failed to support these concepts. Instead, a mainstream of research has been committed on characterizing the newly detected anti-adhesive properties of cranberry products.[6,7]

Adhesion of uropathogenic bacteria like *Escherichia coli* to the urinary tract mucosa is a prerequisite for the pathogenesis of UTI. Bacteria adhere by fimbriae exposing lectins complementary to surface-exposed carbohydrates on the host side tissue,[8] and bacteria differ by the various types of fimbriae that bestow them with more or

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less virulence. Adhesion via type-1 fimbriae, ubiquitously expressed by *E. coli*, is inhibited in the presence of fructose in vitro (hence mannose-sensible fimbriae). More virulent *E. coli* causing pyelonephritis and complicated UTI typically bear p-fimbriae in addition to type-1 fimbriae. Adhesion of p-fimbriated *E. coli* with their specific lectins[9–11] is not inhibitable by fructose or other low molecular carbohydrates (hence mannose-resistant fimbriae).

Cranberry juice or extracts, as well as urine harvested from humans or experimental animals after ingestion of cranberries, reduce the adhesion of *E. coli* and other uropathogenic species in biologically relevant models.[6,7,12–14] The anti-adhesive properties of cranberries are effective against the ubiquitous and comparatively benign *E. coli* with type-1 fimbriae, as well as against p-fimbriated and antibiotic-resistant *E. coli* strains.[14–16] Incubation of p-fimbriated *E. coli* with cranberry juice of neutral pH changes the conformation of surface molecules on p-fimbriae within 2 hours profoundly and the adhesion power gets lost.[17] The conclusion of cranberries as harboring potent anti-adhesive compounds other than fructose had fueled a lively research to identify them.[18]

Howsoever fascinating the exploration of these "gentle" anti-adhesive actions of cranberries are their clinical relevance is not self-evident. Cranberry constituents affect uropathogenic bacteria in more than one way and also disturb their cell integrity. Bacteria exposed to cranberry juice change their shape,[6,19] and the development of p-fimbriae in *E. coli* is suppressed.

Proanthocyanidin (PAC)-standardized cranberry extracts inhibit bacterial growth and biofilm production of *Staphylococcus epidermidis*, *Staphylococcus aureus*, methicillin-resistant *S. aureus*, *Staphylococcus saprophyticus*, and *E. coli.* Extracts inhibit the growth of the Gram-positive bacteria (*Staphylococcus* spp.) with minimum inhibitory concentrations in the range of 0.02–5 mg/mL and inhibit biofilm production. In vitro studies have documented a pronounced effect on bacterial viability and the pathogenetic important production of biofilm by cranberry products.[15,20]

A-type PAC in cranberry products have anti-adhesion activity in vitro

In search for the anti-adhesive constituents in cranberries, a series of elegant experiments identified them as PACs.[21–23] Cranberry PACs are polyphenolic flavanols of various lengths. Those PACs in cranberries with anti-adhesion quality are oligomers of catechin and epicatechin, also classified as condensed tannins. Their units are either linked through single C–C bonds between C_4–C_8 and C_4–C_6 (B-type PACs) or through an additional ether-type bond between C_2–O–C_7 and C_2–O–C_5 (A-type PACs). PACs with at least one A-type linkage account for 50%–90% of PACs in cranberries. Only A-type PAC, restricted to cranberries and a few other plants, have the biological property of inhibiting in vitro adhesion of p-fimbriated *E. coli* to uroepithelial cells. B-type PAC is widely distributed in, eg, green tea, many fruits, or chocolate, but they lack anti-adhesive activity.[23–25] When compared with other plants (eg, ananas, guava, and raisins) cranberries always had a superior anti-adhesion power,[24–27] attributable to their A-type PAC content.[21]

Consecutively, the search for bioactive principles in cranberry products had focused on PAC and specifically A-type PAC. Low bioavailability of flavonoids has been of concern as they may limit or even hinder these compound's health effects. Unfortunately, there are very few data specifically on the bioavailability of A-type PAC. The bioavailability of cranberry anthocyans in general is low. In pharmacokinetic studies, B-type PAC had been poorly intestinally absorbed and had not reached the urinary tract intact.[28] However, other studies suggest an excellent bioavailability of PAC.[29–31]

According to recent research, cranberries are not the only source of botanical anti-adhesion compounds. *Berberis aristata* and the goldenseal (*Hydrastis canadensis*), for example, owe their efficacy against infections to the alkaloide berberine. Berberine reduces the adhesion of uropathogenetic *E. coli* to the mucosa by suppressing the synthesis of fimbriae.[32] Many more plants other than previously supposed harbor macromolecules with anti-adhesion properties. Such molecules are currently investigated for treatment of *Helicobacter pylori*-associated diseases.[33–36]

Currently, however, preventing UTI by anti-adhesion mechanisms is a concept brought forward only for cranberry products. This is reasonable, as there is strong evidence for cranberry-restricted A-type PAC as anti-adhesive compounds, sufficient evidence for PAC bioavailability in humans[29–31] and the preservation of anti-adhesive activity in the urine after oral ingestion.[14,16]

Consequently, recently performed clinical trials have employed cranberry products standardized for their PAC, sometimes even for their A-type PAC content to deliver enough bioactivity to probands or patients. However, the ingested dose of PAC/A-type PAC necessary to inhibit bacterial adhesion in the urine is still unknown. There is no reliable bioassay to measure the appearance and activity of PAC in blood and urine. Some trials have tentatively incorporated serial measurements of anti-adhesion effects in the urine of patients to ensure bioactivity.[14,38] Cranberry products

administered in clinical trials had not been standardized either for PAC or for the crude PAC (36 mg/day[38,39]) or more sophisticatedly even for A-type PAC (9.1 mg/day[39–41] or 18 mg/day[42,43]). In vitro study have suggested that 72 mg/day PAC offers protection against bacterial adhesion in the bladder,[30] others have recommended a daily dose of 36 mg PAC. Thus, in most studies the cranberry products would have been underdosed.

PAC pharmacokinetics in humans had also to be considered. Anti-adhesion activity on bacteria is detectable 2 hours after oral intake of cranberry products, but disappears after 8 hours.[6,14,16,26] Twice or more frequent daily intakes of cranberry products might be necessary to ensure an anti-adhesive effect around the clock.

New data suggest that the content of bioactive PAC is not well controlled in many cranberry products and that its quantification is prone to error. When analyzing 19 commercial cranberry products from the American and European markets for phenolic constituents and in vitro antioxidant capacity and uropathogenic bacterial anti-adhesion some products had been devoid of the relevant flavan-3-ols and some lacking anti-adhesion activity.[44]

Only 4/19 provided the recommended intake of 36 mg PAC/day, but these products would contain as low as 0–205 µg/g A-type proanthocyanidine. Food processing to juice leads to substantial losses of phytochemicals, eg, of >50% anthocyans. The more heat-stable PAC will also be degraded by the higher heat, necessary in processing into powders. Cell wall-bound PAC in cranberries is resistant to conventional methods of extraction – meaning that the content is usually underestimated. These cell wall-bound PACs are still bioaccessible in the human large intestine.

Another neglected variable is the botanical source of the "cranberry products". At least one trial with a positive result had not administered American cranberry (*V. macrocarpon*), but a mixed juice from the European cranberry (*Vaccinium oxycoccus*) and the lingonberry (*Vaccinium vitis-idaea*).[45] New research, refuting older data, proved the putative active compounds to be almost absent in *V. oxycoccus*, but clearly present in lingonberry (*V. vitis-idaea*). Thus, it might be as good to drink lingonberry juice instead of American cranberry juice.[46]

The mixed evidence from clinical trials

Patients potentially benefiting from cranberry prophylaxis range from young women troubled by frequent, but mild UTI over postmenopausal women with more severe recurrent UTI to children and adults with genito-urinary malformations or neurologic diseases suffering from almost permanent and complicated UTI. Within this range, patient's expectations about a prophylactic vary whether they are more or less severely plagued by UTI. Patients with co-morbidities at an increased risk for UTI complications desire a reliable cranberry product to safely replace established prophylactic regimes like antibiotics. For less ill patients, the convenience and attractivity of a natural product may have priority.

In each cohort, various cranberry-based regimens (juice, extracts, with or without PAC standardization, administered once, twice daily or more often, etc) have been studied vs no intervention, placebo, antibiotics, or other prophylactics (see Table 1). Pooled data from these studies have been re-evaluated in meta-analyses. The most recent two meta-analyses have come to different conclusions. While Jepson et al[47] in their Cochrane Review concluded that there was no evidence for cranberries to prevent UTI, Wang et al[48] found a weak evidence after having excluded one trial as a negative outlier.[49] However, critics rightly argued that this maneuver had caused a bias, as data from a positive outlier study had still been analyzed.[50]

Investigators eager to explain negative outcomes of their trials had pointed to unexpectedly low UTI recurrence rates within the chosen observation periods and/or underdosing of the putative active principle. Several trials have indeed missed the calculated UTI recurrence rates necessary to show differences between groups.[49,51,52] In one trial not a single event occurred.[52] This problem should be overcome by recruiting patients with a true high recurrence risk indicated by a pattern of >5 UTI/year rather than on the basis of a recent UTI, as most trials up to now have done. How rewarding this might be is illustrated by a trial with a stratification of patients into a low- and high-risk group at randomization.[42] Many more events occurred in the high-risk group unfolding a significant benefit for cranberry in the high-risk group, but not in the low-risk group.

Strengths and pitfalls of trials are best exemplified by those performed in otherwise healthy young women. UTI in these patients is often related to sexual activity, rarely progressing to pyelonephritis, but nonetheless troubling. Behavioral measures are effective to reduce UTI in this cohort, but cranberry products could be a useful adjunct.

A much cited Finnish trial had impressed with a reduction of the cumulative rate of the first recurrence of UTI by 56% when the young women had drunken 50 mL European cranberry–lingonberry concentrate daily for 6 months.[45] Infection rates had remained lower for 1 year, albeit the juice had only been available for the first 6 months.

Table 1 Clinical trials on cranberry products for UTI prophylaxis

Study population/intervention/design	Result	Publication
Trials mainly in premenopausal women		
Population: 150 young women (mean age 30 years) with previous UTI Intervention: randomization to drink 50 mL European cranberry/lingonberry concentrate daily for 6 months, or to drink 100 mL of a *Lactobacillus* drink 5 days per week for 12 months or no intervention Design: open design with first re-occurrence of symptomatic UTI as study end point	After 6 months, of the 150 women 16% of the cranberry–lingonberry group, 39% of the *Lactobacillus*, and 36% of the control group had a UTI recurrence. Drinking cranberry juice reduced the cumulative rate of the first re-occurrence of UTI by 56% vs control group and the absolute risk for UTI was reduced by 20%	Kontiokari et al[45]
Population: 176 premenopausal women with a recent history of UTI Intervention: cranberry juice 118 ml or 236 ml daily or placebo juice. The PAC content of cranberry juice is not known Design: double-blind placebo-controlled RCT over 6 months. Time to first recurrence of UTI (symptoms + pyuria) was the main outcome. Bacteriuria and bacterial adherence were monthly assessed	Occurrence of UTI in both cranberry groups not different from placebo. Reduction of urinary p-fimbriated *Escherichia coli* strains in cranberry groups	Stapleton et al[38]
Population: 319 college women (mean age 21 years) with a history of UTI Intervention: cranberry juice 236 ml twice daily or placebo juice. The PAC content of the cranberry juice is monitored to be around 112 mg per dose Design: double-blind placebo-controlled RCT over 6 months. End point UTI (symptoms + positive urine culture)	At a lower than expected recurrence rate of UTI (16%) there were no differences between the groups	Barbosa-Cesnik et al[49]
Population: 221 premenopausal women with recurrent UTI Intervention: cranberry capsules (500 mg twice daily – amount of A-type PAC 9.1 mg/g) or TMP-SMX (480 mg once daily) Design: double-blind double-dummy non-inferiority trial over 12 months with primary end points of number of symptomatic UTIs, proportion of patients with at least one UTI, time to first UTI and development of antibiotic resistance	More UTI in cranberry group (4 vs 1.8 in TMP-SMX) and median time to first UTI shorter (4 vs 8 months). Emerging antibiotic resistance in TMP-SMX group An economic evaluation carried out alongside with this trial found higher costs for the cranberry-treated patients without taking into account possible costs related to antibiotic resistance	Beerepoot et al[40] and Bosmans et al[41]
Population: 150 sexually active women (aged 21–72 years) with history of UTI Intervention: consumption of American cranberry juice (250 mL three times per day) or tablets with cranberry extract (two times per day) for 1 year Design: double-blind, placebo-controlled, intent-to-treat design and cost-effectiveness analysis Randomization to three groups: placebo juice + placebo tablets vs placebo juice + cranberry tablets vs cranberry juice + placebo tablets. Outcome measures: >50% decrease in symptomatic UTI per year (symptoms + ≥100,000 organisms/mL) and >50% decrease of annual antibiotic consumption	Both, cranberry juice and tablets decreased the number of patients experiencing at least one symptomatic UTI/year (to 20% and 18%, respectively) compared with placebo (to 32%) ($P<0.05$). The mean annual cost was lower for tablets than for juice	Stothers[53]
Population: 118 patients 20–79 years old, with a history of UTI Intervention: intake of cranberry juice or a placebo beverage (125 mL) once daily before going to sleep Design: RCT double-blinded, over 24 weeks	Less recurrence of UTI with cranberry juice intake in the subgroup of women >50 years	Takahashi et al[55]
Population: 188 pregnant women Intervention: cranberry or placebo in three treatment arms of A-cranberry three times daily, B-cranberry at breakfast then placebo at lunch and dinner, and C-placebo three times daily. After 52 subjects were enrolled, the dosing frequency was reduced to twice daily because of a high withdrawal rate and poor tolerability of the thrice daily dosing regimen Design: randomized controlled trial	There was a 57% and 41% reduction in the frequency of asymptomatic bacteriuria and UTI in the multiple daily dosing group. However, this study was not sufficiently powered at the alpha 0.05 level (CI 0.14–1.39 and 0.22–1.60, respectively, incidence rate ratios). Of 188 subjects 73 (38.8%) withdrew, most for gastrointestinal upset	Wing et al[59]

Trials mainly in postmenopausal women		
Population: 153 elderly postmenopausal women (mean age 78.5 years) Intervention: daily consumption of 300 mL standard cranberry beverage or placebo drink for 6 months Design: double-blind, placebo-controlled trial, no intent-to-treat design. Study groups were compared for the combined occurrence of bacteriuria and pyuria (= infected urine) in 818 urine samples collected at baseline and monthly during the study period	In the cranberry group, the odds for infected urine had been 42% of the odds of the control group. The difference was first detectable after 2 months. The odds for patients with infected urine to remain so was 27% of the control group. Patients in the cranberry group were far more likely to make the transition from infected to non-infected urine There was no acidification of urine by cranberry	Avorn et al[56]
Population: 137 older women with >2 UTI in the previous 12 months Intervention: cranberry extract (500 mg/day) or trimethoprim (100 mg/day). The PAC content of the cranberry extract not known Design: RCT over 6 months. End point UTI (clinical symptoms only)	The risk of recurrence of UTI was 60% higher in the cranberry group (not significantly different). Trimethoprim had a limited advantage, but more adverse effects	McMurdo et al[61]
Population: 928 residents of long-term care facilities (703 women, median age 84) stratified according to UTI risk (long-term catheterization, diabetes, UTI in preceding year) Intervention: cranberry (500 mg with 9 mg PAC) or placebo capsules twice daily Design: double-blind placebo-controlled RCT in two strata based on UTI risk over 1 year with incidence of UTI as primary outcome	No difference was found in participants with low UTI risk (n=413), but in those with a high risk (n=516) the incidence of clinical UTI was lower in the cranberry-treated group (63 vs 85 per 100 person-years at risk) This was true also for a strict definition of UTI. An economic evaluation carried out alongside with this trial did not find the prophylaxis with cranberries to be cost-effective, even not in the high-risk group	Caljouw et al[42] and Van den Hout et al[43]
Population: 367 (mean age 81.5 years) older patients of both sexes in hospitals without previous history of UTI Intervention: daily ingestion of 300 mL cranberry juice or matching placebo beverage for a mean of 18 days Design: randomized, placebo-controlled, double-blind trial. End point: symptomatic UTI	UTI occurred in only 21/376 (5.6%) participants without differences between the groups (14/189 in the placebo group and 7/187 in the cranberry juice group). Infections with *E. coli* were significantly reduced in the cranberry group (13 vs 4)	McMurdo et al[51]
Population: 12 women (25–70 years old) with at least six UTI in the preceding year Intervention: twice daily intake of 200 mg concentrated cranberry extract standardized to 30% phenolics Design: open-label pilot study with 12-week duration of intervention. Follow-up for further 2 years. Recurrence of UTI reported by questionnaire	No UTI occurring during intake; 8/12 women remaining free of infection 2 years later	Bailey et al[52]
Trials in children		
Population: 192 children (85 <1 year, 107 >1 years) with recurrent UTI Intervention: trimethoprim or cranberry, in weight-adapted dosages Design: double-blind observational trial with 75 patients receiving trimethoprim and 117 receiving cranberry over 1 year	Cranberry was not inferior to trimethoprim only in the children >1 year old	Fernández-Puentes et al[62]
Population: 40 children (39 girls) with median age of 7 years Intervention: daily consumption of either cranberry juice with high content in PAC, or cranberry juice without PACs Design: RCT, blinded, for 12 months	65% risk reduction of UTI in the group receiving high PAC cranberry juice vs the juice with no PAC	Afshar et al[58]
Population: 263 children with a history of UTI Intervention: cranberry juice containing 41 g of cranberry concentrate/L 300 mL per day for 6 months Design: double-blind placebo-controlled RCT with an observation period of 1 year	Twenty children in the cranberry group and 28 in the placebo group had at least one recurrent UTI (ns). UTI incidence density per person-year at risk was 0.16 episodes lower in the cranberry group (95% CI, –0.31 to –0.01; P=0.035). The children in the cranberry group had significantly fewer days on antimicrobials (–6 days per patient-year; 95% CI, –7 to –5; P<0.001)	Salo et al[57]
Trials in children and adults with chronic genito-urinary disorders due to malformations or neurologic disease		
Population: 20 children (mean age 7.25 years) with neurogenic bladder caused by myelomeningocele Intervention: placebo or cranberry extract tablets daily Design: RCT, double-blinded, with cross-over design: 6 vs 6 months	Reduction of symptomatic UTI in the cranberry group from 0.5/year (placebo) to 0/year, and also of pyuria	Mutlu et al[66]

(*Continued*)

Table 1 (*Continued*)

Study population/intervention/design	Result	Publication
Population: 171 outpatients with urinary disorders (eg, self-catherization) due to multiple sclerosis Intervention: cranberry extract (36 mg PAC/day) or matching placebo taken twice daily Design: prospective RCT in eight centers over 1 year with primary end point of time to first symptomatic UTI	No difference in time to first symptomatic UTI between cranberry and placebo There had been high drop-out rates and a low rate of UTI during the observation period	Gallien et al[39]
Population: 40 children with neuropathic bladder needing intermittent catheterization Intervention: 15 mL/kg/day cranberry cocktail or water Design: randomized single-blind cross-over study	High drop-out rate, only 21 finished trial. No effect greater than that of water on UTI occurrence	Foda et al[65]
Population: 15 children with neurogenic bladder receiving intermittent catheterization Intervention: cranberry concentrate or placebo concentrate Design: double-blind, placebo-controlled cross-over study for 6 months, change of intervention after 3 months. Urine samples were taken during weekly visits by catheterization, and infection symptoms recorded	No change of the high UTI prevalence of 75% by cranberry juice consumption. *E. coli* remained the predominant pathogen during placebo and cranberry periods	Schlager et al[69]
Population: 15 spinal cord injured patients (mean age 42 years) Intervention: commercial cranberry juice (three times 250 mL/day) Design: pilot study with open cross-over design to determine whether alteration of fluid intake and use of cranberry juice affects influenced biofilm generation. Urine samples investigated for bacterial biofilm load after 7 days drinking three glasses of water daily and after further 7 days of drinking three glasses of cranberry juice daily. Urine samples used to harvest uroepithelial cells to look for biofilm coating and to test for bacterial adhesion	Cranberry juice intake reduced the biofilm load compared with baseline (P=0.013) and the adhesion of Gram-negative (P=0.054) and Gram-positive (P=0.022) bacteria to cells. Water intake had no effect on bacterial adhesion or biofilm presence	Reid et al[68]
Population: 305 spinal cord-injured patients with neurogenic bladder and stable bladder management Intervention: methenamine hippurate 1 g twice daily or 800 mg cranberry extract twice daily, both indistinguishable in taste and appearance Design: double-blind randomized placebo-controlled trial with 6 months follow-up. The main outcome measure was time to occurrence of a symptomatic UTI	Both treatment groups had no longer UTI-free periods than placebo groups (P=0.70 for cranberry; P=0.75 for methenamine hippurate)	Lee et al[67]
Population: persons with spinal cord injury with neurogenic bladder managed by intermittent catheterization or external collection device and bacteriuria. Twenty-six persons received cranberry extract and 22 persons received placebo Intervention: daily ingestion of capsules with 2 g of concentrated cranberry juice or placebo for 6 months Design: randomized, double-blind, placebo-controlled study. Baseline urinalysis and cultures were performed at the time of the initial clinic visit and monthly for 6 months	No differences or trends detected between participants and controls with respect to bacterial counts, types and numbers of different bacterial species, leukocyturia, urinary pH, or episodes of symptomatic urinary tract infection	Waites et al[70]
Trial in renal transplant patients Population: 82 renal transplant recipients with recurrent UTI Intervention: prophylaxis with cranberry juice (two times 50 mL/day, n=39, or L-methionine (three times 500 mg/day, n=25, or both (n=18) vs 30 patients without prophylaxis Design: retrospective analysis of UTI events, pyuria/nitriuria during 1 year before vs after initiation of prophylaxis	Prophylaxis decreased annual UTI by 58% with no change in control group. Cranberry reduced by 64%, L-methionine by 49%	Pagonas et al[77]

Abbreviations: CI, confidence interval; PAC, proanthocyanidin; RCT, randomized controlled trial; TMP-SMX, trimethoprim sulfamethoxazole; UTI, urinary tract infection; ns, not significant.

In a Canadian study, cranberry juice (250 mL three times daily) and cranberry extract in tablets (taken twice daily) had likewise reduced UTI in 150 sexually active women.[53] Contrastingly, the trial by Barbosa-Cesnik et al[49] among college-aged women had failed to find a benefit for a PAC-standardized cranberry juice. Less than expected UTI had occurred during the observation time of 6 months and ascorbic acid in the placebo drink had possibly conferred protection on the control group. In fact, ascorbic acid has an uncertain efficacy in UTI. It is frequently discussed in reviews on UTI, but there is only one trial showing a positive effect in pregnant women.[54]

In the two trials with positive outcomes, high enough UTI recurrence rates had disclosed a benefit for cranberry products within 12 months. Cranberry products of sufficient bioactivity had apparently been chosen and administered at an effective dosing schedule. A high delivery of cranberry bioactivity had been ensured in the Canadian study by three high volume servings of juice or two cranberry tablets daily, while only a once daily serving of 8 oz (=236 mL) cranberry juice had been consumed by patients in the negative trial. The Canadian prescription had obviously been guided by in vitro data on the quickly disappearing anti-adhesion effects of A-type PAC. The success in the Finnish trial can only be explained by a unique quality of the administered juice concentrate. As it reduced UTI recurrence beyond the time of actual exposure, it might have had a longer-lasting influence on bacterial colonization in addition to the short-lived anti-adhesion effect. The juice concentrate made from European cranberries and lingonberries somehow challenges the status of the American cranberry as only botanical UTI prophylactic to work by an anti-adhesion mechanism.

Underdosing, short observation times, and inappropriate selection of patients have all the same accounted for disappointing results of trials performed in elderly postmenopausal women.[51,53,55,56]

To give an example, only 21/376 (5.6%) of hospitalized patients (mean age 81.5 years) had a clinical UTI within a follow-up of 35 days and an intervention period of 18 days in the study by McMurdo et al.[51] At that low event rate, the study time had been too short to find differences, which may well have become evident at a longer study duration. The risk of underdosing has led investigators to apply different doses of cranberry products[38,57–59] or to simply administer the highest available cranberry dose.[60] Wing et al[59] observed a trend toward fewer UTIs in women given higher doses of cranberry juice vs those who received placebo.

There is an imperative demand to establish an optimal in vivo dosage of cranberry products and ongoing studies to determine dose are currently under way.[37] At the same time, investigators are confronted with a surprisingly low acceptability of cranberry products, especially of those with higher PAC contents. Patients had refused taking higher dosages in studies with a dose-finding intention.[37] Withdrawal rates have generally been quite high (up to 55%) in studies, suggesting that cranberry products may not be acceptable over long periods. Complaints about gastrointestinal upset are familiar and explainable from the astringency of higher dosed PAC. In trying to improve palatability of cranberry products, they have often been heavily sweetened with the disadvantage of a high calorie intake and weight gain in patients.

As it is inconvenient taking cranberry products two to three times daily for prolonged periods of time, strong arguments are needed to convince patients to rely on them. Patients will otherwise carry on with drugs like antibiotics and prophylactics, which they often also dislike, but feel safe with. Long-term antibiotics like trimethoprim are an effective way to prevent UTI and three trials have studied cranberry products in head-to-head comparisons with them.[40,61,62] In two trials, more UTI had occurred in the cranberry-treated patients than in antibiotic-treated patients.[40,61] In defend of the failure, underdosing of cranberry bioactivity had been discussed also for these studies. Moreover, the documented rise of antibiotic resistance in the antibiotic-treated patients may have a negative impact on treatment costs in the long run.[41] Cranberry products have the reputation of not driving antibiotic resistance. In a third small trial performed in children, cranberry had not been inferior to trimethoprim.[62]

Another widely discussed advantage of cranberry products over antibiotics is their anti-biofilm efficacy, which had been documented in vitro.[63,64] Biofilms are breeding grounds for bacteria, including multi-resistant strains, and a source for recurrent UTI, eg, in patients with neuropathic bladder dysfunction with indwelling catheters. Unfortunately, studies in this group of patients had controversial outcomes not really encouraging the use of cranberry products.[65–71]

At least three studies have addressed the cost-effectiveness of cranberry products for UTI prophylaxis in association with clinical trials. When taking into account the achieved reduction of spent antibiotics, both tablets of cranberry extract and juice have been found to be cost-effective with a superiority of the tablets in one trial.[32] When compared with trimethoprim sulfamethoxazole, cranberry prophylaxis in premenopausal women had not been cost-effective.[41] However, the potential financial impacts of the observed increased antibiotic resistances in trimethoprim sulfamethoxazole-treated patients had not been taken into account. Even in a trial with a benefit

in patient with high UTI risks, cranberry prophylaxis had not been likely to be cost-effective in the investigated dose, frequency, and setting.[43] The high costs are caused by the recommended uninterrupted daily or even twice daily intake of available cranberry products for prolonged periods of time.

Besides the problems with palatability there are no major safety concerns about cranberry products. In adults, even high amounts of cranberry juice appear to be non-toxic. Infants and young children should restrict the consumption to moderate quantities since they may suffer from gastrointestinal distress and diarrhea. The safety of cranberry products in pregnancy and lactation has been assessed as excellent.[72] More serious adverse effects of cranberry products like drug–cranberry interactions (due to the inhibitory effect of flavonoids on cytochrome P450-mediated drug metabolism) have been reported, but their relevance is questionable. An unreasonable high intake of cranberry juice had caused bleeding in patients treated with warfarin.[73] Beyond this case report an interaction risk with warfarin or other drugs metabolized by cytochrome P450 enzymes had not been confirmed.[74] Cranberry juice had no negative impact on cyclosporin pharmacokinetics in volunteers and in a small retrospective trial in renal transplant patients cranberry products had reduced troublesome UTI without causing safety problems.[75–77] There had been a debate on whether cranberry products were safe in patients with a history of nephrolithiasis, but a relevant pro-lithogenic risk had not been confirmed.[78–80]

Conclusion

The evidence to use cranberry products as an UTI prophylactic is generally regarded as inconclusive.[81,82] According to recent meta-analyses, overall UTI recurrence rates over 1 year could not be reduced by various cranberry products. This is also true for the following separately evaluated subgroups: elderly, pediatric patients, patients with neurogenic bladder, and patients with chronic indwelling urinary catheters.

Cranberry products inhibit bacterial adhesion in biologically relevant models and there is reason to assume that the anti-adhesive quality is specifically attributable to A-type PAC within the anthocyanidin/PAC moieties. This makes it plausible to administer cranberry products rich in anti-adhesive A-type PAC, although it remains uncertain whether clinical outcomes rely on the anti-adhesion effect alone. Further putative effects are related to larger cranberry oligomeric polyphenols with an influence on gut microbiota, but this has not been investigated so far.

By following the currently best hypothesis on how cranberry products may prevent UTI, products should be standardized for a high amount of anti-adhesive A-type PAC. Analytic problems related to measuring the A-type PAC content and their bioavailability in cranberry products need to be overcome to allow comparisons of products, to extrapolate study results, and to establish reliable dosing schemes. Efforts should be made to improve the palatability of cranberry products and to alleviate the inconveniences of current dosing schedules.

Disclosure

The authors report no conflicts of interest in this work.

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