PHYTOTHERAPY RESEARCH
Phytother. Res. **28**: 465–470 (2014)
Published online 6 August 2013 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/ptr.5047

Prevention of Urinary Tract Infections with *Vaccinium* Products

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Cranberries exert a dose-dependent inhibition of the adherence of *E. coli* fimbriae to uroepithelial cells. This was demonstrated *in vitro* but also *ex vivo in vitro* with urine from cranberry consumers. The active principle has not been identified in detail but type-A proanthocyanidins (PAC) play an important role in the mechanism of action. Since the three species, American cranberry (*Vaccinium macrocarpon*), European cranberry (*Vaccinium oxycoccus*) and/or lingonberry (*Vaccinium vitis-idaea*), have different patterns of type-A PACs, results from one species cannot be transferred to the others. It seems likely that most of the studies with monopreparations from *V. macrocarpon* were underdosed. Whereas photometric PAC quantification may overestimate the true content on co-active compounds, reversed phase high-performance liquid chromatograpy may underestimate them. Recent studies with PAC doses in the upper range (DMAC method) or declared type-A PAC content in the daily dose reveal a dose-dependent trend of clinical effectiveness, however, with a possible ceiling effect. In order to clarify this, future three-arm studies should investigate *Vaccinium* preparations with higher type-A PAC doses than previously used. We analysed two popular European *vitis-idaea* products, a mother juice and a proprietary extract. Both preparations may be appropriate to confirm the *Vaccinium* urinary tract infection-preventive effect beyond doubt. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: Vaccinium; urinary tract infection; prevention; cranberry; lingonberry.

Supporting information may be found in the online version of this article (Supplementary Material)

MECHANISM OF ACTION

Attempts to account for the empirically observed prevention of urinary tract infections (UTIs) from cranberry juice have initially focused on urine acidification and bacteriostasis. But both hypotheses were wrong. The pH between urine samples collected after cranberry or placebo consumption did not differ (Di Martino *et al*., 2006), and cranberry juice did not inhibit the growth of the *Gram*-negative *E. coli* species (Monroy-Torres and Macías, 2005; Ermel *et al*., 2012) although inhibiting the growth of *Gram*-positive bacteria (*Staphylococcus spp*.). In a pilot study, antimicrobial activity was noted only against *Klebsiella pneumoniae*, 2–6 h after ingestion of a proprietary preparation from *Vaccinium macrocarpon* (Lee *et al*., 2008). In addition, cranberry juice from this species had no apparent detrimental effect on the vaginal microbiota, but resulted in an apparent loss of potential pathogens from the vagina in almost half of the volunteers (Jass and Reid, 2009).

The key for the mechanism of action of the cranberry active principle was the experiment by Sobota (1984): Cranberry juice inhibited adherence by at least 75% in over 60% of 77 clinical isolates of *Escherichia coli*. Also, urine collected from mice given cranberry juice in the place of their normal water supply for a period of 14 days inhibited adherence of *E. coli* to uroepithelial cells by approximately 80%. Cranberry juice not only affected *E. coli* but also other Gram-negative bacteria (Schmidt and Sobota, 1988). Anti-adherence activity was also detected in the urine of 70% of the subjects, 1 to 3 h after drinking 450 ml of a proprietary cranberry juice. The sugar content and the pH of the juice have been excluded as co-active anti-adherent components (Johnson-White *et al*., 2006). The group of Tao (2011) measured the adhesion forces between a silicon nitride probe and bacteria treated with urine samples with atomic force microscopy. Whereas the adhesion forces of bacteria after exposure to urine collected following cranberry consumption decreased, they did not change after exposure to urine collected following water consumption (Tao *et al*., 2011). The cranberry anti-adhesive effect was reversible and dose-dependent *in vitro* (Pinzón-Arango *et al*., 2009). Two studies demonstrated *ex vivo in vitro* the dose-dependent anti-adhesive activity of the cranberry active principle. In a multi-national placebo-controlled study, a powder with 72 mg proanthocyanidin (PAC) (DMAC method see below) per day had a higher anti-adhesion activity on urine samples *ex vivo* than lower doses (Howell *et al*., 2010). Likewise, a capsule containing a cranberry concentrate with 108 mg PAC per day was more effective than a dose of 36 mg PAC (Lavigne *et al*., 2008). In accordance with this, a dose-dependent trend towards a decrease in bacteriuria

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†Correction added on 15 August 2013, after first online publication. The link for affiliation 3 was removed from Elvira Jungfer's name, as she is not affiliated with that institute.

Received 05 June 2013
Accepted 02 July 2013

plus pyuria, particularly with *E. coli*, was seen in female nursing home residents ingesting cranberry capsules over 1 month. In this short period, the effect of three capsules (108 mg PAC per day) was no better than two capsules (72 mg PAC per day), but both doses were more effective than one capsule (36 mg PAC per day) (Bianco *et al*., 2012). Whether this reflects a ceiling effect remains to be shown.

It has been suggested that an adequate daily dose of cranberry juice should be sufficiently potent to demonstrate urine 'opsonization' of *E. coli* (Chen *et al*., 2013; Tempera *et al*., 2010). There are not yet data available on the spectrum of co-active ingredients excreted in the urine. However, as with anthocyanins glycosides, that may contribute to the clinical symptom-improving effect of cranberry preparaions (Hidalgo et al., 2012), plasma and urine concentrations of the co-active compounds will be very low (Howell, 2007, Milbury *et al*., 2010). In a rabbit model of vesico-ureteric reflux, consumption of cranberries had a protective effect on *E. coli*-induced oxidative renal damage (Han *et al*., 2007).

E. coli, the most frequent urinary isolate from patients with UTIs, is capable of expressing a mannose-specific lectin associated with type 1 fimbriae, which mediates the adherence of the bacteria to uroepithelial cells. In addition, most pyelonephritogenic isolates of *E. coli* express a Gal–Gal-specific lectin associated with P fimbriae, which also mediates the adherence of the bacteria to uroepithelial cells. Cranberry juice was shown to inhibit the adherence of both type 1 and type P fimbriated *E. coli* (Zafriri *et al*., 1989). The anti-adhesive effect is based on molecular-level changes in the surfaces of fimbriated *E. coli* (Liu *et al*., 2006). Cranberry juice may disrupt bacterial ligand–UC receptor binding (Liu *et al*., 2008) by decreasing nanoscale adhesion forces between fimbriated *E. coli* and uroepithelial cells (Liu *et al*., 2010). A bioassay has been introduced for testing the adherence of P-fimbriated *E. coli* to a human uroepithelial cell line (Turner *et al*., 2005). It has been suggested that cranberry juice decreases bacterial biofilm formation (Chen *et al*., 2013; Wojnicz *et al*., 2012). Cranberry extracts inhibited the biofilm production by Gram-positive bacteria (*Staphylococcus* spp.) but did not eradicate the biofilm (LaPlante *et al*., 2012). In accordance with this, a recent study indicated that the effect of cranberry juice in preventing UTIs is not explained by mechanisms that reduce biofilm formation or the expression of selected virulence genes of *E. coli* in urine (Tapiainen *et al*., 2012). Cranberry compounds inhibited bacterial motility via downregulation of the flagellin gene (Hidalgo *et al*., 2011).

ACTIVE PRINCIPLE

The cranberry active principle, which is the sum of all compounds that contribute to the cranberry effects, has not yet been identified. There is no doubt that PACs, in particular type-A PACs play an important role (Foo *et al*., 2000a,2000b; Howell *et al*., 2005; Ermel *et al*., 2012; Gupta *et al*., 2012). Foo and co-workers (2000b) have isolated various compounds of which three A-type trimers from *V. macrocarpon* prevented adherence of P-fimbriated *Escherichia coli* isolates from the urinary tract to cellular surfaces containing receptor sequences similar to those on uroepithelial cells. Procyanidin A2 showed only a weak anti-adherence activity whereas the monomer epicatechin and procyanidin B2 were inactive. Commercially available preparations labelled as cranberry products can be produced from American cranberry (*Vaccinium macrocarpon*), European cranberry (*Vaccinium oxycoccus*) and/or lingonberry (*Vaccinium vitis-idaea*), as monopreparations or mixtures. The three species differ in their PAC pattern. The sum of A-type dimers and trimers was higher in lingonberry (*Vaccinium vitis-idaea*) than in the American cranberry (*Vaccinium macrocarpon*) and was lowest in the European cranberry (*Vaccinium oxycoccus*). The three berry species contain different A-type dimers and trimers. For example, *V. macrocarpon* contained about 4.5 mg and *V. vitis-idaea* (origin Europe) 2.1 mg of procyanidin A2/100 g, but *V. vitis-idaea* had an additional 5.9 mg/100 g of another A- type PAC that is rare in *V. macrocarpon* (about 0.15 mg/100 g). Provided that A-type trimers are the most important for the anti-adherent activity, it remains to be established if all of the eight A-type isomers found in the different berries (Jungfer *et al*., 2012) are equally effective or differ in the anti-adherent effectiveness. Most studies on UTI used monopreparations from *V. macrocarpon*. The three trimers identified as having anti-adherence activity (Foo *et al*., 2000b) occurred in much higher concentrations in *V. macrocarpon* than in *V oxycoccus* and *V. vitis-idaea*. Due to the different A-type PAC pattern in the different species (Jungfer *et al*., 2012), the results obtained with the *V. macrocarpon* active principle cannot be transferred to the other species. More research is necessary to focus on the differences between the active priciples of *V. macrocarpon, V. oxycoccu*s and *V. vitis-idaea* and other co-active compounds such as anthocyanins and their metabolites (Hildago *et al*., 2012).

Fresh berries of *V. vitis-idaea* contain around 20 mg type-A PAC per 100 g (Hänsel *et al*., 1994). The amount of co-active anthocyanins varied according to the area of harvest (Lee and Finn, 2012). It depends therefore on the starting material (berry species, harvest area), how much of the active principle to be found in cranberry products. PAC losses may occur during manufacturing and storage (Boudesocque *et al*., 2013).

PACs can be quantified by photometric methods, such as Pharmacopeia method (Wittig *et al*., 2002), or by more specific assays called PAC003-DMAC or BL-DMAC (Prior *et al*., 2010). The latter method uses 4-dimethylamino-cinnamic-aldehyde as colouring reagent that reacts with PAC and creates a colour. This colour is then measured to calculate the concentration of PAC, which can then be translated into a percentage. Both photometric methods do not measure specifically the A-type PACs but the sum of all PACs in the sample. A high reading of total PAC does not mean a high reading of A-type PAC and, even if it did the detailed pattern of A-type PACs cannot be deduced from the photometric result. The DMAC method favours the low molecular weight PAC as dimers and trimers. Total PAC estimates obtained with the pharmacopeia method are, depending on the reference standard used, more than 50% higher than those obtained with the DMAC assay. Both DMAC assays provide similar results; the advantage of the BL-DMAC method is its feasibility.

By means of the reversed phase (RP) high performance liquid chromatograpy (HPLC) method, dimeric and trimeric PAC can be separated and detected

individually and A-type PACs can be distinguished from B-type PACs, whereas no specific RP-HPLC quantitation is possible for higher polymeric compounds. This means that A-type PAC quantification by RP-HPLC underestimates the total A-type PAC content of a cranberry product. A comparison between the high performance thin layer chromatography densitometry and the DMAC method revealed that the latter overestimated the total PAC concentration, because the DMAC method includes – possibly inactive – degradation products as well (Boudesocque *et al*., 2013). HPLC after thiolysis includes the polymeric PACs, but it is just the total that is determined without information about the molecular composition. In addition, the double-linked A-type PAC dimers are resistant to thiolysis and trimers so that A-type PACs are only partially thiolyzed (Karchesy and Hemingway, 1986). HPLC after thiolysis will therefore underestimate the quantity of A-type PAC in a cranberry product.

When 19 different commercially available cranberry products have been analysed, a dose of 36 mg total PACs/day (DMAC method) provided zero up to 0.2 mg A-type PAC dimers and trimers in the daily recommended dose, indicating the lack of product standardization and incongruence between global and individual compound analyses (Sánchez-Patán *et al*., 2012). A compromise has therefore been suggested that cranberry PAC should be measured by using recent advances in liquid chromatography coupled with mass spectrometry and production of PAC standards (Krueger *et al*., 2013). Such analyses showed that the (underestimated) amount of type-A PACs in the daily dosage may vary between 0.05 and 20 mg (sum of dimers and trimers) (Hofmann *et al*., 2010). Nowadays, sophisticated techniques (e.g. MS/MS detection) together with co-active ingredients as reference substances should be used for detailed characterization of the products used in clinical studies (see below).

EVIDENCE OF EFFECTIVENESS OF CRANBERRY PRODUCTS

The empirically observed effectiveness of cranberry products for the prevention of UTIs has been questioned in a recent Cochrane review (Jepson *et al*., 2012), which did not find that cranberry juice decreased the number of symptomatic UTIs over a 6 or 12 months period. The authors concluded that cranberry juice cannot currently be recommended for the prevention of UTIs, and that, for other preparations (such as powders), further data are needed to demonstrate effectiveness.

There is, however, evidence in more recent studies that the cranberry active principle may well be a useful phytomedicine for the prevention of UTIs. The reduction in urinary P-fimbriated *E coli* strains supports the biological plausibility of the cranberry activity. The mechanism of action is convincing and the effect dose dependent. Thus, it should be only a question of dose to show in a confirmatory study that a high dose cranberry product is better than placebo in producing a clinically relevant preventative effect. We suspect that most of the cranberry products tested in the studies included in the recent Cochrane review (Jepson *et al*., 2012) were underdosed. We have therefore summarized the recent clinical trials investigating cranberry products with declared amounts of PAC >36 mg (DMAC method) or type-A PAC amounts in the daily dose.

Studies with PAC declaration according to the DMAC method

Among young women with an acute UTI, those drinking cranberry juice with 224 mg PAC daily did not experience a decrease in the 6-month incidence of a second UTI, compared with those drinking a placebo (Barbosa-Cesnik *et al*., 2011). Cranberry juice with 56 mg or 112 mg PAC per day did also not significantly reduce UTI risk compared with placebo. The potential protective effect observed in terms of a reduced proportion of women with P-fimbriated urinary *E coli* isolates during the intervention phase (cranberry juice group 44%, placebo group 80%) was consistent with previous studies and warrants confirmation in larger, well-powered studies of women with recurrent UTIs (Stapleton *et al*., 2012). In children, cranberry juice containing up to 96 mg PAC per day in up to 300 ml, the intervention did also not significantly reduce the number of children who experienced a recurrence of UTI, but it was effective in reducing the actual number of recurrences and related antimicrobial use (Salo *et al*., 2012). This was also consistent with previous studies and warrants confirmation in larger, well-powered studies that include children. It remains to be seen whether entero-coating protects PACs from being metabolized before being absorbed and results in higher PAC urine concentrations (achieved with lower PAC doses, Bonetta and Di Pierro, 2012). In the pilot studies by Takahashi *et al*. (2012) and Afshar *et al*. (2012), the adult patients with multiple UTI relapses and children received 125 ml cranberry juice (about 50 mg PAC per day) or 2 ml/kg cranberry juice (PAC 37% as stated in the article), respectively. Both studies showed a trend of effectiveness. Since the amount of type-A PACs has not been declared in any of the products used in these studies, further data are needed to find the optimum dose based on type-A PACs for the prevention of UTIs.

Studies with PAC declaration according to HPLC data

Sengupta *et al*. (2011) investigated a proprietary cranberry extract with 7.5 and 15 mg/day PAC (sum of type-A and type-B PAC). Since HPLC after thiolysis was employed, the sum probably underestimated the type-A quantity. Since in general the amount of A-type PAC exceeds that of B- type PAC (Jungfer *et al*., 2012), one might assume that the amount of A-type PAC in the daily dose was below 5 and 10 mg, respectively. The daily DMAC PAC dose was reported as 2 mg. At the end of the 90-day treatment period, change in the presence of E. coli in the untreated control group was not significant, whereas, there was significant reduction in the subjects positive for *E. coli* in both the high dose and low dose treatment groups, compared to baseline evaluation. Symptomatic relief was also reported in the low and high dose treatment groups, while none was reported by subjects in the untreated control group. The authors concluded that the proprietary extract was effective in safely reducing the number of *E. coli* positive subjects at

Table 1. Content of type-A PACs (mg procyanidin A2 equivalents/100 ml juice or 100 mg extract (two measurements) and content of PAC as assessed with the photometric DMAC assay; nd = not detectable; DRD daily recommended dose; [a]as described in Jungfer *et al*., 2012.

RP-HPLC Compounds[a]	Juice mg/100 ml	Granulate mg/100 mg
A Dimer 1	2.65 / 3.46	21.2 / 22.5
Procyanidin A2	0.76 / 0.94	17.9 / 17.9
A Trimer 1	1.97 / 2.30	3.9 / 4.2
A Trimer 2	nd	nd
A Trimer 3	0.87 / 1.00	5.1 / 5.7
A Trimer 4	1.16 / 1.20	5.7 / 5.3
A Trimer 5	1.00 / 1.22	2.6 / 2.9
A Trimer 6	1.78 / 1.98	9.0 / 8.0
A Trimer 7	0.33 / 0.46	2.6 / 2.6
A Trimer 8	0.53 / 0.50	3.3 / 2.9
DRD	**mg/30 ml**	**mg/10 g**
Sum of A Dimers	1.17	3.97
Sum of A Trimers	2.46	3.19
Sum of A Di- and Trimers	**3.63**	**7.2**
DMAC	**mg/30 ml**	**mg/10 g**
PAC	44.9 / 43.7	88.4 / 87.8

both the 500 mg and 1000 mg dose levels and in ameliorating the symptoms of UTI in these subjects. Again, this could indicate a ceiling effect.

Beerepoot and coworkers (2006) investigated a proprietary cranberry concentrate with 9 mg type-A PAC in the daily dose in premenopausal women. Trimethoprim-sulfamethoxazole 480 mg once daily was more effective than cranberry capsules 1000 mg daily to prevent recurrent UTIs – but at the expense of emerging antibiotic resistance. Antibiotic resistance did not increase in the cranberry group. The same cranberry preparation but half dose (500 mg) had been tested against cranberry juice 750 ml and placebo (Stothers, 2002). In this exploratory study, both cranberry preparations were more effective than placebo in decreasing the number of patients experiencing at least one symptomatic UTI/year and total annual antibiotic consumption was less in both cranberry treatment groups. Cost effectiveness ratios demonstrated cranberry tablets were twice as cost effective as organic juice for prevention. Also in another study carried out in children suffering from neurogenic bladder complaints 500 mg of this proprietary extract per day over 6 months decreased the bladder infection rate and pyuria (Mutlu and Ekinci, 2012). All three studies showed a trend of effectiveness for a daily cranberry doses between 5 and 10 mg type-A PAC in the daily dose. Poor compliance with juice is a problem in long-term use of these cranberry products (Jepson *et al*., 2012). An appropriate cranberry extract may help increase patient compliance.

PUTATIVE STUDY MEDICATIONS AND FUTURE ASPECTS

The Swiss cranberry market is dominated by products from *Vaccinium vitis-idaea* which is less well investigated than *Vaccinium macrocarpon* but which is more popular than the latter in Europe. We used the BL-DMAC (Prior *et al*., 2010) and the RP-HPLC (Jungfer *et al*., 2012) methods to quantify the PAC and type-A PAC contents in the daily proposed dosages of two lingonberry (*V. vitis-idaea*) products: A pure juice (mother juice, daily dose 30 ml per day prepared from 34 g ripe berries, Biotta, Switzerland) and a granulate with a proprietary extract (daily dose 10 g/day prepared from 50 g ripe berries, Alpinamed, Switzerland) dissolved in water. Details of the methods and of the results may be found in the online version of this article or on the webpage: (www.uniklinik-freiburg.de/rechtsmedizin/live/forschung/phytomedicine/originalartikel.html) and in Table 1.

According to the DMAC method, the granulate contained double the PAC amount (about 90 mg) in the daily dosage compared to the juice (about 45 mg) which does, however, not necessarily mean that the granulate contained more active principle (see above). A PAC content of about 180 mg in 10 g of granulate had previously been found (Krähenmann, personal communication). However, for comparison, the products need to be compared in the same DMAC assay procedure. Our RP-HPLC results reveal that, in 30 ml of the proprietary lingonberry juice, the total type-A PAC dose was about half (3.7 mg) of that found in 10 g of extract (about 7 mg). The juice contained relatively less A dimers (about one third) compared to the extract. Since the anti-adhesive effectiveness of A dimers and A trimers has not been compared, further studies are required to elucidate the active principles in the two products. Using an HPLC method that differed in the detection technique (UV instead of MS/MS) and in the reference substance (catechin instead of procyanidin A2), 20 mg type-A PAC had been identified in 10 g of the proprietary granulate by the Hofmann group (2010). Because of the higher specificity of the MS/MS detection method, the HPLC method we used should be employed in the future, so as not to overestimate the quantity of the active principle. For comparison, products need to be quantified by the same assay procedure.

The guidelines of the European Association of Urology suggest that, because of possible adverse events and concern about selecting resistant pathogens, antimicrobial prophylaxis should be considered only after counselling, behavioural modification and non-antimicrobial measures have been attempted (Wagenlehner *et al*., 2013). Cranberry products with an appropriate dose of active principle have, therefore, a place in the treatment of UTI prevention. We suggest that future studies investigate cranberry products with higher type-A contents than previous studies. The two lingonberry preparations seem to be appropriate for such a study. For example, a daily dose of Biotta juice 120 ml (14.8 mg of type-A PAC) versus 60 ml (7.4 mg of type-A PAC) and/or a daily dose of Alpinamed extract 20 g (14.4 mg of type-A PAC) versus 10 g (7.2 mg of type-A PAC) versus placebo may be compared. A similar study should also be carried out with the American cranberry (*V. macrocarpon*). Such studies could rule out or confirm a ceiling effect. At least two confirmatory studies are warranted to demonstrate good evidence of clinical effectiveness. Because of the different A-patterns, any health claims arising should apply only to the particular *Vaccinium* product studied and at the appropriate dose. The product may then be optimized by removing three triterpenes (maslinic acid, corosolic acid, and ursolic acid) identified as CYP3A inhibitors provided they are not part of the active principle (Kim *et al*., 2011). Otherwise CYP3A inhibition needs to be considered in patients treated with other CYP3A inhibitors.

Conflict of Interest

None of the authors has a conflict of interest.

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