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Vaccinium macrocarpon: An interesting option for women with recurrent urinary tract infections and other health benefits

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Abstract

Aim: To review the scientific publications concerning the clinical use and mechanism of action of the North American cranberry (*Vaccinium macrocarpon*) for women with recurrent urinary tract infections (UTI) and other health conditions.

Methods: This is a retrospective study of published information concerning *Vaccinium macrocarpon* retrieved from a PubMed and individual searches.

Results: Urinary tract infections are very common in women, cause discomfort, and may aggravate other genitourinary conditions. The available scientific information supports a clinical benefit of *Vaccinium macrocarpon* in the prevention of recurrent UTI in women. There is a non-significant reduction of UTI associated with *Vaccinium macrocarpon* treatment during pregnancy. A group of proanthocyanidins (PAC) with A-type linkages have been isolated from *Vaccinium macrocarpon* which inhibit P-fimbriae synthesis and induce a bacterial deformation, on both antibiotic-susceptible and antibiotic-resistant uropathogenic *Escherichia coli*. It is plausible that cranberry PAC prevent bacteria from adhering to the uroepithelium of the bladder, thereby blocking the ability of *E. coli* to infect the urinary mucosa.

Conclusion: Cranberry treatment is a safe, well-tolerated supplement that does not have significant drug interactions. Although investigations are in the early stages, experimental and preclinical studies suggest that cranberry components may have other potential benefits, including anti-infective, anticancer and antioxidant effects, which may be considered as positive for different age-related conditions. In addition, cranberry components may induce positive cardiovascular and metabolic changes, and may improve neuropsychological activity. These effects warrant further clinical research to better place the role of cranberry products for women.

Key words: American cranberry, proanthocyanidin, urinary tract infection, *Vaccinium macrocarpon*.

Introduction

A urinary tract infection (UTI) is often considered a minor illness, yet it can cause severe discomfort. The infection has been widely studied during pregnancy, the postpartum period and after genital surgery. It is also common in postmenopausal and elderly women; the estimated incidence may range from 4 to 15%,[1] with

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a significant increase in relation to age.[2,3] In light of the fact that more people are reaching advanced age and hence their needs are increasing concomitantly, UTI are becoming increasingly important. Additionally, mortality in women with a history of UTI has been reported to be higher than in the age-matched controls.[4]

Uncomplicated UTI involves the urinary bladder in a host without underlying renal or neurological disease. Bladder infections are more common in women than men by virtue of the shortened urethra. Cystitis represents bladder mucosal invasion, most often by enteric coliform bacteria (e.g. *Escherichia coli*) that inhabit the periurethral vaginal introitus and ascend into the bladder through the urethra. Bacteria may be harboured in the urinary bladder epithelium and trigger a recurrent infection.[5] Urine is generally a good culture medium; factors unfavourable to bacterial growth include a low pH (5.5 or less), a high urea concentration, and the presence of organic acids that enhance acidification of the urine. Frequent and complete voiding has been associated to a reduction in the incidence of UTI. In normal conditions, although a thin film of urine remains in the bladder after it is voided, the remaining bacteria is eliminated by mucosal cell organic acid production. When the mechanisms fail, upper tract or kidney involvement occurs in the form of pyelonephritis. Moreover, among women who have experienced a UTI, an increase in urine loss occurs in the immediate post-UTI period, when compared to infection-free periods.[3] Leaving the clinical relevance aside, the financial cost related to UTI is enormous.[6]

The increasing prevalence of UTI caused by antibiotic-resistant bacteria makes any empirical treatment more difficult, especially in a high-risk population like elderly women. Overtreatment and antibiotic resistance are becoming increasingly common, and undertreatment also poses a threat of complications. Herbal and probiotic medicines have been proposed as alternative treatments for recurrent UTI. Proanthocyanidins (PAC) are polyphenolic metabolites widely distributed in higher plants and have been associated with potential positive health benefits, including antibacterial and chemotherapeutic activities.[7] The role of North American cranberry (*Vaccinium macrocarpon*), a significant source of PAC, for the prevention of postmenopausal UTI and other age-related health conditions will be reviewed in the present document taking into account the most relevant scientific information obtained from a PubMed and individual searches.

Table 1 Factors contributing to susceptibility of postmenopausal and elderly women to recurrent urinary tract infections (UTI)

Postmenopausal women
Lack of estrogen
Non-secretor status
A history of UTI in the premenopausal period
Urinary incontinence
Presence of a cystocele
Post-void residual urine
Sexual intercourse
Diabetes mellitus
Institutionalized women
Catheterization
Urinary incontinence
Antimicrobial exposure
Functional status

Recurrent UTI Risk Factors in Women

Urinary tract infections during pregnancy are very prevalent and have significant risks for both the mother and fetus.[8–10] Although extensively studied in younger women, risk factors for UTI among postmenopausal and elderly women have been described less frequently (Table 1). Older women may not present to the clinician with typical UTI symptoms, hence the accuracy of a clinically-based diagnosis is often uncertain. In contrast, low UTI symptoms are difficult to distinguish from those of painful bladder syndrome and overlap with those of interstitial cystitis, chronic urethral syndrome, overactive bladder and vulvodynia.[1] Misdiagnosis of lower UTI in the older population may contribute to the development of complicated infections that require advanced and costly therapeutic interventions. Like younger women, postmenopausal women with current UTI are more likely to be sexually active and have a history of UTI. Epidemiological evidence and several case reports suggest that *E. coli* causing UTI may be transmitted between sex partners. Thus, uropathogenic *E. coli* (UPEC) are more likely than commensal *E. coli* to be shared with a current heterosexual sex partner.[6] UPEC strains are associated with almost six times the odds of being shared, and sharing is even greater if the uropathogen had P pili. The higher rates of UPEC vaginal colonization among women with UTI might also be explained by the greater quantities of *E. coli* and the proximity of the urethra to the vagina.

Postmenopausal and elderly women with bladder or uterine prolapse have an increased frequency of UTI due to incomplete bladder emptying that eventually

allows residual bacteria to overwhelm local bladder mucosal defenses. Anatomic factors are strongly associated with recurrent UTI: urinary incontinence, presence of a cystocele, and post-voiding residual urine. Thus, multivariate analysis has shown that urinary incontinence, a history of UTI before menopause, and non-secretor status were most strongly associated with recurrent UTI.[11] Minor abnormalities of the lower urinary tract may be relevant in a small number of patients with UTI. Postmenopausal and elderly women are also more likely to have diabetes mellitus and to be incontinent. High urine glucose content and the defective host immune factors found in patients with diabetes mellitus and other metabolic conditions may also predispose to infection. These abnormalities include immunologic impairments and local complications related to neuropathy, such as impaired bladder emptying. Also, higher urine glucose concentration may serve as a culture medium for pathogenic microorganisms. However, women with diabetes have a higher risk of UTI in relation to diabetes duration and severity but not to recent glucose control.[12] Although patients with diabetes mellitus more often received initial longer and more potent antibiotic treatment than those without diabetes, postmenopausal women with diabetes mellitus more often had recurrences of UTI.

The usual UTI treatment is a short course of antibiotics. The initial therapy is empiric, based on the knowledge of the predominant pathogens and their antimicrobial susceptibility. Cystitis can be cured with 2 or 3 days of antibiotic therapy while pyelonephritis requires a longer course of treatment. Nevertheless, one of the relevant factors contributing to the high resistance rates might be the indiscriminate use of antibiotics. Fluoroquinolone-sparing agents, such as nitrofurantoin and fosfomycin, have shown to be alternative therapies by further clinical efficacy and safety studies.[13] However, frequent recurrent UTI occur despite appropriate initial therapy and negative follow-up urine cultures.[6]

Vaginal flora alterations in postmenopausal women may modify the risk of UTI. Heavy growth of *lactobacilli* is associated to a lower frequency of vaginal colonization with *E. coli*.[14] Antibiotics often eliminate lactobacilli, along with harmful bacteria that cause an overgrowth of *E. coli* in the vagina. Thus, it seems that taking antibiotics for a UTI increases the risk of a subsequent infection. Hormone replacement therapy and topically applied intravaginal estrogen would reduce the incidence of recurrent UTI. The hormone effect might be related with *Lactobacillus* colonization that normalizes vaginal pH. However, there is evidence that hormone therapy does not reduce the rate of UTI.[15]

Uropathogenic *E. coli*

Uropathogenic *E. coli* causes 90% of UTI in unobstructed urinary tracts. Uroepithelial bladder exfoliation, through an apoptosis-like process, initiates as a consequence of uropathogenic binding, probably as a protective response of the host in order to eliminate the bacteria. In addition, UPEC initiates an invasion through the epithelium in an attempt to evade the immune system. The role of this internalization process in response to treatment and the risk of recurrence remain to be determined. UPEC have several attributes that are lacking in the commensal *E. coli*. They carry chromosomal gene clusters on 'pathogenicity islands', encoding adhesins and other virulence factors. The most important of these are probably the adhesins that aid bacteria in the uroepithelium adherence process.[16] These include type 1, S- and P-fimbriae. P-fimbriae has a terminal receptor for the 'P' antigen (or pyelonephritis-associated pili) that contains a D-galactose-D-galactose residue. This antigen is a blood group marker which binds not only to red cells, but also to a specific galactose dissaccharide that is also found on uroepithelial cells and the surface of cells lining the vagina and the perineum.[17] Approximately 75% of the population expresses the P antigen, and these individuals are particularly susceptible to UTI. This antigen is also found in vaginal and prostatic secretions which are protective because they bind to the bacterial receptor, preventing binding of the UPEC to the surface epithelium. Individuals most susceptible to UTI would be those who express P antigen on their cells and lack P antigen in their secretions.[16]

Mammalian response to *E. coli* in the urinary tract also includes the production of pro-inflammatory cytokines, such as interleukin-6 and interleukin-8.[18] The latter molecule is key to attracting neutrophils to the site of infection. The interactions between UPEC and elements of the innate immune response determine the outcome of an infection. It is not known why bacteriuria causes cytokine release that results in symptoms in some cases and not in others. Persistence of UTI has been also related with biofilm formation by the most frequent microorganism involved. *In vitro* production of biofilm is more frequent among strains causing relapse.[19] The use of therapeutic compounds that eliminate biofilm-forming *E. coli* could

prevent subsequent relapses. *E. coli* adhere more to the uroepithelial cells of diabetic women, either because of substances excreted in the urine or because of a difference in the uroepithelial cells. *In vitro* studies indicate that the number of type 1-fimbriated *E. coli* that adhered to cells is double in uroepithelial cells from diabetic women compared to cells from control subjects.[20]

Vaccinium macrocarpon in UTI Prevention

A significant body of research has established that the dietary intake of berry fruits has a positive impact on human health, performance and disease.[7] Native Americans used cranberries (*Vaccinium macrocarpon*) for food and also as a red dye. The ripe fruit of the cranberry is the part of the plant most commonly used for medical purposes. Cranberries are composed mostly of water (approximately 80 to 88%) and carbohydrates (approximately 10%).[21] Flavonoids, anthocyanins, catechin, triterpenoids, organic acids and ascorbic acid are the other existing constituents that make up the remaining 10%.[22] Cranberry products, either juice or tablets, have been used for decades as an alternative medicine to prevent UTI and the ammoniacal odor of urine. In recent years, as problems with antibiotics are increasing and the biology of UPEC is detailed, there is a new interest in the *Vaccinium macrocarpon* properties.

Clinical evidence concerning cranberries in UTI

Clinical and epidemiological evidence support the role of *Vaccinium macrocarpon* in maintaining urinary tract health. Avorn *et al*.[23] conducted the first well-controlled clinical trial demonstrating that regular drinking of cranberry juice reduced the presence of bacteria in the urine, and the effect was not related to more acidic urine. Baseline urine samples, followed by monthly ones, were taken over the 6 months of the study. The results showed that bacteriuria and pyuria occurred in 28% of the placebo group, in comparison to only 15% of women in the cranberry juice group.

Table 2 presents the clinical studies considered in the meta-analysis by Jepson and Craig[24] and some other publications on the matter. The meta-analysis included eight randomized controlled trials (RCT)[22–26,29,30,33] and two quasi-RCT,[23,25] available at January 2007. The studies included 1049 participants of all ages who received either cranberry products (juice, tablets or

Table 2 Subjects and clinical characteristics of studies included in the Jepson and Craig meta-analysis[24] and other studies

Authors	*n*	Subject clinical characteristics
Included in the meta-analysis		
Avorn *et al*.[23]	192	Elderly women, mean age 78.5 years
Haverkorn and Mandigers[25]	38	Elderly men ($n = 9$) and women ($n = 29$), mean age 81 years
Foda *et al*.[26]	40	Children (mean age 9.35 years) with neuropathic bladder requiring clean intermittent catheterization
Walker *et al*.[27]	19	Young women (median age 37 years) with recurrent UTI
Schlager *et al*.[28]	15	Children (aged 2–18 years) with neuropathic bladder requiring clean intermittent catheterization
Kontiokari *et al*.[29]	150	Young women (mean age 29–32 years) with previous UTI
Stothers[30]	150	Women (aged 21–72 years) with recurrent UTI
Linsenmeyer *et al*.[31]	21	Spinal cord injury patients with neuropathic bladders
Waites *et al*.[32]	48	Spinal cord injury patients with neuropathic bladders
McMurdo *et al*.[33]	376	Elderly inpatients in rehabilitation hospital wards
Other UTI-related studies not included in the meta-analysis		
Di Martino *et al*.[34]	20	Healthy volunteers (10 men and 10 women)
Bailey *et al*.[35]	12	Women (aged 25–70 years) with a minimum of six UTI in the preceding year
Bohot[36]	120	Women (aged 18–65 years, mean age 35.7 years) with a minimum of three UTI in the preceding 6 months
Other studies		
Duthie *et al*.[37]	22	Healthy women
CrewS *et al*.[38]	50	Community-dwelling volunteers ≥60 years
Valentova *et al*.[39]	65	Healthy young women

cranberry capsules), placebo juice or water for at least 1 month for the prevention of UTI. Three studies included young women,[27,29,30] three studies evaluated elderly men and women,[23,25,33] and four studies evaluated individuals who had spinal cord injuries.[26,28,31,32] Treatment with cranberry product reduced the incidence of UTI at 12 months compared with the placebo/control subjects, and were more effective in women with recurrent UTI than elderly men and women or individuals requiring catheterization. The authors concluded that cranberries may decrease the number of UTI episodes over a one-year period. Dropouts or withdrawals were high in several studies probably due to the taste and high cost of treatment.

There are other UTI-related studies not included in the meta-analysis supporting the beneficial urinary cranberry effects (Table 2). Di Martino *et al*.[34] studied the effects of cranberry juice on UPEC biofilm formation in a small human population. Bailey *et al*.[35] carried out an open label study in women with a history of UTI to evaluate the effects of a daily dose of concentrated cranberry extract for 12 weeks, confirming the prevention of UTI in the following two years. To study postcoital-related UTI, Bohbot[36] randomized women who suffered three episodes of UTI in the previous 6 months, to receive a postcoital single dose, within 6 h, of either PAC (36 mg), cranberry total components, or placebo. The response was more significant in the group treated with all cranberry components as compared to either placebo or PAC treatments during 45 days duration of the study. It seems that some component, different to PAC, may also contribute to the UTI cranberry preventive effect.

There is limited information concerning the safety and efficacy of cranberry during pregnancy. In a survey of women from Norway, the authors found that cranberry was the most commonly used herbal treatment during pregnancy and there was no evidence of safety or harm to the fetus.[40] A recent RCT evaluated the use of daily cranberry juice for the prevention of asymptomatic bacteriuria in pregnancy, showing a non-significant 57 and 41% reduction in the frequency of asymptomatic bacteriuria and all urinary tract infections, respectively, when used at a three-times daily dosing schedule.[41] There are no reports concerning cranberry use during lactation.

There are relevant publications (Table 2) concerning other possible health benefits of cranberries, including anti-infective effects, atherosclerosis prevention, and tumour growth inhibition.[37–39] However, some *in vitro* effects have not been confirmed *in vivo*.[42]

Cranberry mechanisms of action against urinary bacteria

No definitive mechanism of action has been identified to explain the potential effects of cranberries in UTI prevention. In 1923, Blatherwick and Long[43] proposed that cranberry acidity produces an antibacterial effect in the body, but this theory was later disproved. Cranberries may have a number of health benefits, the foremost being their anti-adhesion effect on certain urinary bacteria.[44] These properties seem to be specific to some of the components of cranberry that are not present in orange, pineapple, mango, guava, green tea, chocolate, apple and grape fruit juice.[45,46] Cranberries contain three different flavonoids (flavonols, anthocyanins and PAC), catechins, hydroxycinnamic and other phenolic acids, and triterpenoids. Vaccinium fruits are among the most abundant food sources of anthocyanin, although content varies widely among cranberry cultivars, averaging 25–65 mg/100 g of ripe fruit at harvest.[47]

The main anthocyanins are absorbed into the human circulatory system and transported intact in the urine. Cranberry products do not inhibit bacterial growth and will not sterilize the urinary tract, although they prevent bacterial adherence to uroepithelial cells, thus reducing the development of UTI. No dose-response studies have been performed to determine the optimal dose to prevent infection. The efficacy mechanism can be traced in the patient's urine following an oral intake of cranberry juice. Urinary levels of anthocyanins reached a maximum between 3 and 6 h after ingestion of cranberry, and the recovery of total anthocyanins in the urine over 24 h is estimated in 5% of the amount consumed.[44] Highly acidic conditions are not necessary for the prevention of bacterial adhesion.[22] The anti-adhesion effects of P-fimbriated UPEC to uroepithelial cells are related with A-linked PAC as compared with the lack of anti-adhesion activities of B-linked PAC from grape and apple juices, green tea and dark chocolate in human urine following consumption of each food product.[48] The A-type linkage in cranberry PAC would enhance both *in vitro* and urinary bacterial anti-adhesion activities. The PAC fraction binds to the most potent lipopolysaccharide, a major component of the outer membrane of Gram-negative bacteria. It seems that the most potent lipopolysaccharide-binding activity is contained within a PAC fraction composed of polymers with an average degree of polymerization of 21.[49] When *E. coli* grows in the presence of cranberry components for long periods of time, the morphology

of the bacteria changes, initially from a rod shape and subsequently to a more spherical cell-like form. These changes also cause them to be repelled by human cells.[50]

In vitro bacteria adherence is significantly higher to vaginal epithelial cells from women with recurrent UTI than from controls. *In vivo*, vaginal fluid significantly alters the adherence of type 1 piliated *E. coli* to epithelial cells.[17] Cranberry powder and increasing PAC extract concentrations inhibited adherence of *E. coli* to vaginal epithelial cells in a dose-dependent linear relationship.[51] This vaginal effect may be relevant both for the prevention of UTI and for the maintenance of the normal vaginal ecosystem, although clinical studies are required.

Urine from subjects who received cranberry capsules showed a significant reduction in bacterial adherence to these cells compared to placebo. In addition, a significant dose-dependent decrease in bacterial *in vitro* adherence was encountered after cranberry consumption. In an *in vivo* model, using the same urine, it was confirmed that *E. coli* strains had a reduced ability to kill *Caenorhabditis elegans* after growth in the urine of patients who consumed cranberry capsules.[52] Another potential mechanism of action against UPEC is the non-enzymatic generation of nitric oxide (NO) by dismutation of nitrite to NO and NO_2 under mildly acidic conditions.[53] 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.[54]

The consumption of cranberry juice may prevent the adhesion of antibiotic-resistant P-fimbriated UPEC to the uroepithelium. All these findings may lead to new therapeutic strategies to prevent the rising problem of bacteria antibiotic resistances. The effectiveness of cranberry PAC has been also reported against antibiotic-resistant *E. coli.*[55]

Other Possible Health Benefits of Cranberry

Cranberry polyphenols inhibit biofilm formation, and disrupt acid production and glucan-mediated biofilm development by oral microorganisms.[56,57] Additionally, cranberry components may also effect extracellular enzyme production and activity in gingival fibroblasts and macrophages.[58] These effects may open new insights for the treatment of periodontitis and the development of cariostatic preventive measures and other oral hygienic approaches to prevent biofilm-related oral diseases.

In vitro cranberry anti-adhesion properties on *Helicobacter pylori* have allowed the design of a randomized clinical study to evaluate a possible additive effect to the conventional triple therapy. In women, the eradication rate was higher in the cranberry-conventional arm than in the placebo-conventional arm and significantly higher than in the non-placebo-conventional group.[59] In addition, regular consumption of cranberry juice can suppress *H. pylori* infection in endemically afflicted populations.[60] In addition, there are preliminary preclinical evidences regarding cranberry non-specific antiviral effects.[61]

Cranberry polyphenols and flavonoids may reduce atherosclerosis risk by increasing the resistance of low density lipoprotein (LDL) to oxidation, inhibiting platelet aggregation, reducing blood pressure, and by anti-thrombotic and anti-inflammatory mechanisms.[62,63] Cranberries are also responsible for the induced expression of LDL receptors, and the increased uptake of cholesterol in hepatocytes.[64] In healthy humans, the consumption of a low-calorie cranberry juice is associated with a favorable postprandial glycemic response that may be beneficial for individuals with impaired glucose tolerance.[65] Within 1 week of regular consumption of cranberry juice there is an increasing salicylic acid absorption[37] that may benefit health in some individuals.

A 6-week double-blind, placebo-controlled, randomized, clinical study carried out in older adults, aged 60 years or above, who reported no history of dementia or significant neurocognitive impairments (Table 2), demonstrated in the cranberry treated group a non-significant trend in their overall abilities to remember as compared to placebo controls.[38]

Cranberry phytochemicals inhibit the growth and proliferation of breast, colon, prostate, lung, and other tumors, as do flavonols, PAC oligomers, and triterpenoids isolated from the fruit. Possible mechanisms of action include induction of tumor cell apoptosis, reduction of ornithine decarboxylase activity and matrix metalloproteinases expression, and inhibition of cyclooxygenases.[66–69] Preliminary *in vitro* results demonstrated in ovarian cancer cells resistant to platinum that drugs became up to six times more sensitized after exposure to cranberry juice extracts in comparison to cells that were not exposed.[70]

Wild berries of the *Vaccinium* species have antioxidant properties. Radical scavenging and antioxidant activities are attributable to their composition of catechins and procyanidins.[71] Drinking cranberry juice for the 4 months duration of the study increased plasma superoxide dismutase activity and reduced nitrate and nitrite, and malondialdehyde concentrations in castrated rats.[72] It has been proposed that the protective effect of cranberry may be related to a decrease in nitrate and nitrite concentrations and dose-dependent decrease in peroxidation. In healthy women, consumption of cranberry juice significantly increased plasma antioxidant capacity, attaining a maximum after 60–120 min.[73] Consumption of cranberry juice for 2 weeks did not alter blood or cellular antioxidants or several biomarkers of lipid status relevant to heart disease.[39] Another study[42] demonstrated, however, that an 8-week high dose of cranberry juice resulted in a statistically significant difference in serum levels of oxidation protein products (Table 2).

Precautions with Cranberry Treatment

No side-effects have been associated with consuming multiple servings or supplements of cranberry products. However, cases of upset stomach have been reported after consumption of very large daily amounts of cranberry juice. Cranberries contain oxalates which may contribute to the formation of some types of kidney stones.[74] Nevertheless, the ingestion of cranberry juice decreased oxalate and phosphate excretion while citrate excretion increased,[75,76] suggesting antilithogenic properties, which deserves consideration as a conservative protocol for the management of calcium oxalate urolithiasis. Case reports suggest that the use of supplemental cranberry products is not recommended for individuals who take warfarin;[77] however, their consumption did not increase their anticoagulant effect.[78] No other interactions have been reported between cranberries and prescription drugs, non-prescription drugs, other herbal supplements, or foods.

Final Remarks

Urogenital infections in women remain problematic. After menopause, vaginal pH increases, lactobacilli disappear from the vaginal flora, and the vagina is predominantly colonized by *Enterobacteriaceae*, especially *E. coli*. In postmenopausal and elderly women, UTI predisposing factors are difficult to be corrected and long-term antibiotic prophylaxis is not devoid of complications. *Vaccinium macrocarpon* may be considered with significant effects on UPEC and a wide spectrum of positive action on some other health frequent complaints. The availability of limited and heterogeneous research indicates that the consumption of cranberries seems to prevent recurrent UTI. Most laboratory researches agree that cranberries do possess natural compounds that could possibly prevent urinary tract infections.

Although doubts exist regarding the best cranberry presentation or dose (i.e. sweetened or unsweetened, tablet or extract juice, and duration of treatment) that must be consumed in order to yield the most positive results, a reference dosage is one or two daily doses of either 36 mg PAC or equivalent cranberry total components, for 1–2 months. It is recommended to be accompanied with a high water intake.

Answers to the many questions concerning the real value of *Vaccinium macrocarpon* in maintaining urinary tract health should be obtained from prospective controlled studies comparing this therapy with standardized conventional prophylactic therapy. The results from the ongoing 'non-antibiotic versus antibiotic prophylaxis for recurrent urinary-tract infections' (NAPRUTI) study should provide insights on the topic.[79] Nevertheless, the Guideline on Urinary Tract Infections from the European Association of Urology already includes cranberry products among the alternative prophylactic methods of managing recurrent uncomplicated UTI in women.[80]

Additionally, experimental and preclinical studies support anti-infective, metabolic and anticarcinogenic cranberry effects which might be positive side-effects in women. Cranberry use could ameliorate these free-radical-producing conditions related to immune function suppression and cellular damage. It can be speculated that cardiovascular disease, degenerative diseases, and cancer may be ameliorated in some way by cranberry components. However, much more research is required to prove or disprove if these effects are significant for humans.

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