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Review Article

Safe Treatment of Urinary Tract Infections by American Cranberry

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Abstract:

Cranberry fruit (Vaccinium macrocarpon) grows on evergreen shrubs that are native to North America. Cranberry is a term derived from the contraction of ‘‘crane berry.’’ This name is derived from the nickname of the bilberry flower, which, when it withers, is similar in appearance to the head and neck of the sand crane, a bird that often feeds on the berries of this plant. The cranberry is part of the Ericaceae family and naturally grows in acidic swamps full of peat moss in humid forests. Cranberries are composed of water (88%), organic acids (including salicylate), fructose, vitamin C (high levels, i.e., 200 mg/kg of fresh berries), flavonoids, anthocyanidins, catechins, and triterpinoids. The chemical constituents responsible for their taste are the iridoid glycosides. The anthocyanidins and proanthocyanidins (PAC) are tannins (stable polyphenols) found only in vaccinium berries and function as a natural plant defense system against microbes. Common preparations with cranberries include fresh, whole berries, gelatinized products, juices (usually 10-25% pure juice) and capsules. Pure juice is too acidic (pH, 2.5) and unpalatable, even with sweeteners .Despite cranberry presentation, it is generally recommended to consume cranberries just prior or two hours after meals; it is also important to drink lots of water, mainly after preparations from dehydrated juices. Cranberry juice, predominantly in the form of a juice cocktail drink with approximately 25% cranberry juice, has been the traditional choice of most women seeking to prevent Urinary Tract Infections (UTIs). American cranberry has a complex and rich phytochemical composition, particularlyflavan-3-ols, A-type procyanidins (PACs), anthocyanins, benzoic acid, and ursolic acid. Cranberryflavan-3-ols are present as monomers, oligomers, and polymers). These oligomers and polymers are also referred to as PACs or condensed tannins and representw85% of the total flavan-3-ols on a weight basis.

Cranberry is the main source of peonidin among 100 foods commonly consumed in the United States. Quercetin 3-galactoside is the predominant form, but at least 11 other glycosides are present in lower concentrations. Some of these, such as quercetin-3-acetylrhamnoside are rare in berries. In the Phenol Explorer database, the flavonol content of plant foods is usually <3 mg/100 g FW, although bilberry, black-berry, and blueberry contain 3.2–17 mg/kg. Cranberry fruit is classed as a functional food due to the naturally high content of compounds, such as polyphenols, which are believed to have antioxidant and therefore health-promoting properties. Health benefits of cranberry consumption range from cardio protective effects due to improved cholesterol profiles to aiding digestive health. Cranberry exists in various forms, including the raw fruit (fresh and dried), cranberry juice and cranberry extract in capsule/tablet formulations. Cranberry extract could be a potential alternative to antibiotics to treat acute uncomplicated UTIs. Proanthocyanidin (PAC) with A-type linkages, or their metabolites, is believed to be the active ingredient in cranberry, preventing Escherichia coli (E. coli) from binding to the bladder uroepithelium and thereby reducing the ability of E. coli to cause and sustain a UTI. Cranberries have also been found to improve lipid profile, improve endothelial function, and lower several markers of cardio metabolic risk. Nowadays, growing evidence suggests an important role of cranberries in maintaining digestive health. In addition to the anti-inflammatory effects, cranberries may also influence intestinal barrier integrity, which is another essential element of intestinal health. Cranberry was reported as the main source of peonidin among 100 foods commonly consumed in the United States.

However, in the majority of studies, the total anthocyanin content is re-ported rather than amounts of individual anthocyanins. This approach may change because the bioavailability and health effects of anthocyanins seem to be affected by the structures of the aglyconesor the glycosidicmoieties . Quercetin 3-galactoside is the predominant form, but at least 11 other glycosides are present in lower concentrations. Some of these, such as quercetin-3-acetylrhamnoside are rare in berries. As shown in the Phenol Explorer database, the flavonol content of plant foods is usually <3 mg/100 g FW, although bilberry, black-berry, and blueberry contain 3.2–17 mg/kg.

Key words: anthocyanidins; catechins; triterpinoids; proanthocyanidin and anthocyanin

Introduction

Cranberry is a term derived from the contraction of ‘‘crane berry.’’ This name is derived from the nickname of the bilberry flower, which, when it withers, is similar in appearance to the head and neck of the sand crane, a bird that often feeds on the berries of this plant (Guay, 2009). The cranberry is part of the Ericaceae family and naturally grows in acidic swamps full of peat moss in humid forests (Bruyere, 2006). The American cranberry (Vaccinium macrocarpon) was historically used by North American Indians to treat UTIs (Guay, 2009). There are other relatives of the cranberry family (European cranberry – V. oxycoccus; lingonberry – V. vitisidaea; blueberry – V. myrtillus) that share some of the cranberry’s basic components, but research evidence for a role in prevention is limited (Kontiokari *et al*., 2001 and Jepson and Craig, 2007).

Cranberries are composed of water (88%), organic acids (including salicylate), fructose, vitamin C (high levels, i.e., 200 mg/kg of fresh berries), flavonoids, anthocyanidins, catechins, and triterpinoids (Guay, 2009). The chemical constituents responsible for their taste are the iridoid glycosides. The anthocyanidins and proanthocyanidins (PAC) are tannins (stable polyphenols) found only in vaccinium berries and function as a natural plant defense system against microbes (Guay, 2009 and Cimolai and Cimolai, 2007).

Common preparations with cranberries include fresh, whole berries, gelatinized products, juices (usually 10-25% pure juice) and capsules (Guay, 2009; Bruyere, 2006; Kontiokari *et al*., 2001; Jepson and Craig, 2007; Gupta *et al*., 2007 and Di Martino *et al*., 2006). Pure juice is too acidic (pH, 2.5) and unpalatable, even with sweeteners (Guay, 2009).Despite cranberry presentation, it is generally recommended to consume cranberries just prior or two hours after meals; it is also important to drink lots of water, mainly after preparations from dehydrated juices (Bruyere, 2006). Cranberry juice, predominantly in the form of a juice cocktail drink with approximately 25% cranberry juice, has been the traditional choice of most women seeking to prevent Urinary Tract Infections (UTIs). Cranberries have been tested for their clinical relevance in many different conditions. They have been evaluated in the treatment of UTIs but were deemed ineffective (Cimolai and Cimolai, 2007 and Lavigne *et al*., 2007).

Cranberries were also studied for UTI prophylaxis chiefly in women, but also in children and men; additionally, they have been studied in conditions such as neurogenic bladder and pregnancy, (Kontiokari *et al*., 2001; Stothers, 2002; Barbosa-Cesnik *et al*., 2011; McMurdo *et al*., 2005; 2009; Wing *et al*., 2008; Lee *et al*., 2007; McGuinness *et al*., 2002; Waites *et al*., 2004 and Ferrara *et al*., 2008). Most clinical interest in the use of cranberries is for cystitis prevention. In the 2008 Cochrane Database of Systematic Reviews, there were ten randomized trials regarding UTI prevention on a total of 1,049 patients. They concluded that there is some evidence that cranberry juice may decrease the number of symptomatic UTIs over a 12 month period, particularly, and only, for women with recurrent UTIs (Jepson and Craig, 2008).Whereas berries are noted simply as good sources of potassium or fiber, recent research suggests that berry fruits are a rich source of numerous phytochemicals with a broad array of bioactivity and an impact on human health (Paredes-López *et al*., 2010; Côté *et al*., 2010; Basu and Lyons, 2012; Wang *et al*., 2012 and Kaspar and Khoo, 2013).

The American cranberry (Vaccinium macrocarpon) is a particularly rich source of (poly)phenols, which have been associated in vitro with antibacterial, antiviral, antimu-tagenic, anticarcinogenic, antitumorigenic, antiangiogenic, anti-inflammatory, and antioxidant properties (Côté *et al*., 2010; McKay and Blumberg, 2007 and Del Rio *et al*., 2013). In vivo, animal models reveal that cranberry extracts can reduce C-reactive protein (CRP) and proinflammatory interleu-kins and increase NO synthesis (Kim *et al*., 2011); decrease angiotensin-converting enzyme, angiotensin II, and angiotensin II type 1 receptor (Yung *et al*., 2011); suppress Helicobacter pyloriinfection (Xiao and Shi, 2003); and improve pancreaticb-cell glucose responsiveness and functionalb-cell mass (Zhu *et al*., 2011). Some of these actions may un-derlie the results from clinical studies showing that cranberry products can lower LDL cholesterol (LDL-C) and total cholesterol (Lee *et al*., 2008), increase HDL cholesterol (HDL-C) while lowering the oxidative modification of LDL-C (Ruel et al., 2006), improve endothelial function (Dohadwala *et al*., 2011 and Flammer *et al*., 2011), lower glycemic responses (Wilson *et al*., 2010), elevate plasma antioxidant capacity (Ruel *et al*., 2005; Duthie *et al*., 2006 and Vinson *et al*., 2008), modulate ulcerogenic gastric H. pyloricolonization (Gotteland et al., 2008 and Shmuely *et al*., 2007), decrease cariogenic Streptococcus mutans and total bacterial counts in saliva (Weiss et al., 2004), reduce biomarkers of metabolic syndrome (Basu and Lyons, 2012 and Basu *et al*., 2011), and protect against urinary tract infections (UTIs) (Wang et al., 2012 and Vasileiou et al., 2013).

American cranberry has a complex and rich phytochemical composition, particularlyflavan-3-ols, A-type procyanidins (PACs), anthocyanins, benzoic acid, and ursolic acid. Cranberryflavan-3-ols are present as monomers, oligomers, and polymers) (Pappas and Schaich, 2009). These oligomers and polymers are also referred to as PACs or condensed tannins and representw85% of the total flavan-3-ols on a weight basis (White *et al*., 2011and Gu *et al*., 2004).

Cranberry was reported as the main source of peonidin among 100 foods commonly consumed in the United States (Wu *et al*., 2006). However, in the majority of studies, the total anthocyanin content is re-ported rather than amounts of individual anthocyanins. This approach may change because the bioavailability and health effects of anthocyanins seem to be affected by the structures of the aglyconesor the glycosidicmoieties(Crozier *et al*., 2010 and Czank *et al*., 2013).Quercetin 3-galactoside is the predominant form, but at least 11 other glycosides are present in lower concentrations (Pappas and Schaich, 2009 and Côté *et al*., 2008). Some of these, such as quercetin-3-acetylrhamnoside are rare in berries (Mikulic-Petkovsek *et al*., 2012). As shown in the Phenol Explorer database, the flavonol content of plant foods is usually <3 mg/100 g FW, although bilberry, black-berry, and blueberry contain 3.2–17 mg/kg (Mikulic-Petkovsek *et al*., 2012 and Harnly *et al*., 2006).

The other species are blueberry (Vaccinium angustifolia) and bil-berry (Vaccinium myrtillus). Cranberry typically grows in bogs and is a member of the same family as blueberry and bilberry. Massachusetts and Wisconsin are the main areas of present-day commercial production of cranberry (Nova Scotia Department of Agriculture and Fisheries, 2004). Cranberry has been found to specifically inhibit hemagglutination of E.

coli by expression of types (Nova Scotia Department of Agriculture and Fisheries, 2004) and P adhesion through the component compounds fructose and proanthocyanidins.In the United States, one of every five women has been reported to have a lifetime incidence of UTI. Of these women, 3 percent experience recurrent disease. Eleven million women receive medication for UTIs annually (Foxman *et al*., 2000).A recent Cochrane Database systematic review Jepson et al. (2004) found no randomized trials assessing the effectiveness of cranberry juice in the treatment of UTIs and concluded that there is no evidence to support its use. There is much greater evidence-based information available for the use of cranberry in UTI prophylaxis.A Cochrane Database systematic review, Jepson et al. (2004) citing small sample sizes and the poor quality of available trials, determined that there was no reliable evidence of effectiveness of cranberry in UTI prophylaxis.

However, since 2001, two good-quality studies have been published. The first trial18 of 150 women consisted of three arms: (Nova Scotia Department of Agriculture and Fisheries, 2004) cranberry/lingon berry juice, pro-biotic supplementation with Lactobacillus GG drink; and no intervention for 12 months. Findings were a statistically significant 20 percent reduction in absolute risk of infection in women receiving cranberry (number needed to treat: 5) compared with no effect in the probiotic-supplementation and no-intervention groups (Kontiokari *et al*., 2001).Most recently, a randomized, placebo-controlled trial, a single experimental study showed that the "high-molecular-weight constituent" of cranberry juice that inhibits the adherence of E. coli was effective in reversing and inhibiting the coaggregation of a large portion of dental plaque bacteria. Cranberry also has been recommended as an adjunctive treatment for Candida infections (Stothers, 2002). A small study found a significant rise in urinary oxalate levels, prompting a caution that regular use of cranberry may increase the risk of kidney stone formation in patients with a history of oxalate calculi (Terris *et al*., 2001).

Cranberries have historically been associated with urinary tract health, particularly among women with rUTIs (Raz *et al*., 2004; Guay, 2009 and Pérez-López *et al*., 2009). Results from several clinical studies have suggested that cranberries may decrease rUTIs in healthy women (Guay, 2009; Vasileiou *et al*., 2013; Caljouw *et al*., 2014; Stapleton *et al*., 2012 and Takahashi *et al*., 2013). In addition, in vitro and ex vivo research has suggested that cranberry-derived compounds such as A-type proanthocyanidins and other polyphenols may interfere with adhesion of bacteria (including multidrug-resistant Escherichia coli) to epithelial cells of the urinary tract, attenuate the development of uropathogen reservoirs (i.e., in the gastrointestinal tract and intracellular pods within the urothelium), and sup-press inflammatory cascades (Vasileiou *et al*., 2013; Gupta *et al*., 2012 and Blumberg *et al*., 2013).

Specifically, a meta-analysis by Wang and colleagues published in 2012 concluded that "cranberry products were associated with protective effects against UTIs (RR: 0.62; 95% CI: 0.49, 0.80), particularly for women with Recurring Urinary Tract Infections (*rUTIs*) (RR: 0.53; 95% CI: 0.33, 0.83)" (Wang *et al*., 2012). In contrast, a meta-analysis by the Cochrane Collaboration, also published in 2012, concluded that ".cranberry juice is less effective than previously indicated. Cranberry juice cannot currently be recommended for the prevention of UTIs" (Jepson et al., 2012). It is interesting that the Cochrane analysis was an up-date of a 2008 report that resulted in a conclusion similar to that derived by Wang et al., indicating a shift in the conclusions from this group (Jepson *et al*., 2008 and 2012).In theory, meta-analysis of results from randomized clinical trials examines the consistency of data across studies and is considered to be the strongest level of evidence that guides relevant practice decisions (Melnyk, 2004).

Cranberry fruit (*Vaccinium macrocarpon*) grows on evergreen shrubs that are native to North America (Polashock *et al*., 2014). Cranberry fruit is classed as a functional food due to the naturally high content of compounds, such as polyphenols, which are believed to have antioxidant and therefore health-promoting properties (Szajdek and Borowska, 2008). The reported health benefits of cranberry consumption range from cardio protective effects due to improved cholesterol profiles (Ruel *et al*., 2006) to aiding digestive health (Pappas *et al*., 2009). Cranberry exists in various forms, including the raw fruit (fresh and dried), cranberry juice and cranberry extract in capsule/tablet formulations (Bodet *et al*., 2008). Cranberry extract could be a potential alternative to antibiotics to treat acute uncomplicated UTIs. Proanthocyanidin (PAC) with A-type linkages, or their metabolites, is believed to be the active ingredient in cranberry, preventing Escherichia coli (E. coli) from binding to the bladder uroepithelium (Howell et al., 2005) and thereby reducing the ability of E. coli to cause and sustain a UTI. Systematic reviews assessing the use of cranberry in the management of recurrent UTIs provide mixed evidence for benefit (Wang *et al*., 2012 and Luís *et al*., 2017). A 2012 Cochrane review of 24 trials (n = 4473) of men, women and children found that cranberry did not significantly reduce recurrent UTI compared with placebo, advice to increase water intake or no treatment. A subgroup analysis of women with recurrent UTI found that cranberry consumption resulted in a non-significant reduction in recurrent UTIs (Jepson et al., 2012). Whilst many studies have evaluated the effectiveness of cranberry extract in reducing recurrent UTI, few have assessed effects on symptoms of acute UTIs (Vicariotto, 2014).Cranberries for the prevention of UTIs in susceptible populations are examined in another review by the same authors (Jepson and Craig, 2008).

Cranberries are among a few foods that contain A-type proanthocyanidins. Unlike B-type proanthocyanidins, A-type proanthocyanidins have an additional ether interflavan bond between C2→O→C7 (Prior and Gu, 2005).It was suggested that A-type proanthocyanidins have greater bioactivity compared to B-type (Howell *et al*., 2005).Two recent studies suggested that cranberry oligosaccharides might also play a role in preventing UTIs because xyloglucan oligosaccharides were found to be a new cranberry bioactive component with E. coli anti-adhesion] activity (Hotchkiss *et al*., 2015 and Sun *et al*., 2015).

Cranberries have also been found to improve lipid profile, improve endothelial function, and lower several markers of cardio metabolic risk (Paquette *et al*., 2017; Lee *et al*., 2008 and Novotny *et al*., 2015). Nowadays, growing evidence suggests an important role of cranberries in maintaining digestive health (Anhe *et al*., 2015 and Denis *et al*., 2015).Two 250 mL bottles of cranberry juice daily for 90 days was found to suppress H. Pylori infection in the stomach of susceptible population (Zhang *et al*., 2005). In addition to the anti-inflammatory effects, cranberries may also influence intestinal barrier integrity, which is another essential element of intestinal health (Contreras *et al*., 2015 and Pierre *et al*., 2014).

In the early 2000s, Kontiokari et al. (2001) and Stothers et al. (2002) investigated the effects of cranberry juice or tablets, respectively, on UTI prevention. The subjects were healthy, sexually active women, aged 21–72 years, with a history of UTI. Both studies showed a significantly decreased number of patients experiencing at least one episode of UTI per year. In a very recent randomized, double-blind, placebo-controlled, multicenter clinical trial, 28373healthywomen with a recent UTI history were recruited to consume a 240 mL low-calorie cranberry juice cocktail daily for 24 weeks. Cranberry juice consumption significantly reduced the number of UTIs by 39%.

Urinary tract infection is a common bacterial infection in children (Habib, 2012). One serving of 50 mL cranberry juice was given to the children to drink once per day for 6 months (Ferrara et al., 2009). This trial had a relatively large sample size (n=84) and low dropout rate, 3.5% in the cranberry group versus 6.8% in the control group. Cranberry juice, with or without proanthocyanidins, was randomly assigned to 40 children for one year (Afshar *et al*., 2012). A 65% reduction in the risk of UTIs was obtained during a 12-month follow up. The compliance level was 70% for

both groups. Both studies suggested that cranberry juice was effective in preventing the recurrence of pediatric UTI. Salo et al. (2012) conducted a double-blinded randomized placebo-controlled trial in 2012.

A 2008 Cochrane review, (Jepson and Craig, 2008) which included five cross-over and five parallel designed studies, reported that cranberry products significantly reduced the incidence of UTIs at 12 months compared to the placebo/control group. Cranberry-containing products were found to be associated with preventative effects on recurrent UTIs in another systematic review of 13 randomized controlled trials (Wang *et al*., 2012).The most recent meta-analysis and trial sequential analysis evaluated 28 clinical trials and concluded that the use of cranberry products significantly reduced the incidence of UTIs (Luis et al., 2017). However, meta-analysis in the 2012 Cochrane review36concluded that cranberry products did not significantly reduce the occurrence of symptomatic UTI overall compared to placebo, water, or no treatment. This review had substantial heterogeneity in the results.

Several factors contribute to the conflicting results obtained from clinical trials. The major factors are low compliance due to the as tringency and bitterness of cranberry juice, high withdrawal rate, inconsistency of dosage, and lack of standardization of cranberry content in testing products. Cranberry capsules were used to overcome the undesired taste of cranberry juice. However, in two trials using cranberry capsules, the withdrawal rates were more than 40%, partly due to the side effects (Linsenmeyer *et al*., 2004 and Waites *et al*., 2004). Quite a few trials were not randomized, double blind, or placebo controlled, or had short duration time (less than 6 months). In addition, the optimum dosage and formulation were not established in previous studies (Guay, 2004).

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