American Herbal Pharmacopoeia®
and Therapeutic Compendium

Cranberry Fruit

Vaccinium macrocarpon Aiton

Revision

Standards of Analysis, Quality Control, and Therapeutics

Editors

Roy Upton RH DipAyu
American Herbal Pharmacopoeia®
Scotts Valley, CA

Thomas Brendler
PlantaPhile
Collingswood, NJ

Research Associates

Diane Swisher MA
American Herbal Pharmacopoeia®
Scotts Valley, CA

Lynette Casper BS
Planetary Herbals
Scotts Valley, CA

Marta V Correll MS LAc
American Herbal Pharmacopoeia®
Scotts Valley, CA

Michael Mazur
Maryland University of Integrative Health
Laurel, MD

oxidants in healthy adults. Additionally, the presence of PAC A2 dimers was observed for the first time and occurred after the flavonoids and phenolics to similarly varied degrees (T_{max} in four subjects at 10 h; 2 subjects between 10–24 hours; and one subject at 2 h).

In a study of Valentova et al. (2007), dried cranberry juice (1200 mg/d) was given in capsules (200 mg/per capsule) to volunteers for 8 weeks. An increase in urine levels of total phenols, hippuric, salicyluric, and dihydroxybenzoic acids and quercetin glucuronide was observed. Liu et al. (2015) reported an increased excretion of hippuric acid and plasma citric acid levels after consumption of a cranberry juice concentrate (57% juice) by 18 healthy female subjects. The authors suggest these metabolomic changes may contribute to the putative health benefits attributed to cranberry.

Pedersen et al. (2000) reported a small but significant (P <0.05) increase in total phenols in plasma within 1 hour of consumption of 500 mL of cranberry juice cocktail (Ocean Spray®) compared to either blueberry juice or a control (sugar water) in human subjects (n = 9). Interestingly, even though blueberry juice had a higher amount of total phenols (2589 µg gallic acid equivalent [GAE]/mL) compared to those in cranberry juice (893 µg GAE/mL), only the cranberry juice showed a significant increase in plasma phenol levels and a significant increase (P <0.001) in antioxidant capacity of plasma as determined by both ESR spectroscopy and change in FRAP value. No change in urine levels of total phenols up to 4 hours after drinking was observed.

Other human investigations with single subjects offer additional pharmacokinetic information. In an assessment by Zhang and Zuo (2004), a single subject consumed 1.8 L of cranberry juice cocktail (Ocean Spray; 27% juice). Benzoic acid, *o*-hydroxybenzoic acid, 2,3-dihydroxybenzoic acid, ferulic acid, and sinapic acid were detected in plasma 45 minutes after drinking, with benzoic acid predominating at 4.40 and 3.11 µg/mL at 45 and 270 min, respectively. Interestingly, two phenolic acids, *p*-hydroxyphenylacetic and 2,4-dihydroxybenzoic acid, have been identified in plasma after cranberry juice consumption, but not in the juice itself. These researchers did not analyze metabolites in urine.

Animal Studies

In rats fed 3 different levels of a cranberry concentrate powder (Prior et al. 2010a), urinary excretion of 3-hydroxycinnamic, 4-hydroxycinnamic, 3,4-dihydroxybenzoic, and 3-hydroxybenzoic acids increased in a linear manner with increased dietary intake of the cranberry powder. For most phenolic acids, the percentage of phenolic acids excreted in the conjugated form was approximately constant across levels of cranberry in the diet and ranged from 65 to 100% for the individual phenolic acids. However, a few phenolic acids were excreted only in the free form while others were nearly completely conjugated. Thus, measurement of just the free form may not accurately reflect the amount excreted. Future studies investigating the health effects, bioactivity, or bioavailability of parent polyphenols should also consider the contribution of their metabolites, not just the parent compound(s). Relative to feeding blueberry, black raspberry, or cranberry, the greatest increase in the excretion of phenolic acids with cranberry feeding was observed in hippuric acid (HA), 4-hydroxycinnamic acid (4HCA), and 3-methoxy, 4-hydroxybenzoic acid (VA) (Khanal et al. 2013). Older literature indicates that cranberry consumption resulted in the formation and excretion of hippuric acid (Bodel et al. 1959). The authors suggested that hippuric acid is formed by the transformation of quinic acid, possibly carried out by intestinal bacteria. In one of the early cranberry pharmacokinetic studies, Blatherwick and Long (1923) found that the consumption of 305 g of cranberry sauce by a single subject increased hippuric acid in the urine from a basal value of 0.78 to 4.74 g. Later, however, Kubota and Ishizaki (1991) demonstrated that benzoic acid is excreted in the urine as hippuric acid. Benzoic acid is present in whole cranberry juice products but may not be present in other preparations. Benzoic acid has strong antibacterial activity. Hippuric acid has been shown to reduce the saturation of urinary calcium oxalate with a potential beneficial effect on reducing stone formation (Atanassova and Gutzow 2013).

Seed Oils

Cranberry seeds contain a number of oils with potential health benefits (e.g., antioxidant effects), including high levels of (-)-linolenic acid (30.9 g/100 g fat), tocopherols, and tocotrienols (Parry et al. 2006; Yu et al. 2005). No data exist on the pharmacokinetics of cranberry seed oils. However, Burton et al. (1988) reported that the mid-gut is the site of greatest tocopherol absorption in rats. Hayes et al. (1993) found that tocotrienols were deposited along with triglycerides in the adipose tissues of hamsters. Tocopherols were the only tocol readily detected in all tissues except adipose during tocotrienol supplementation in hamsters. Thus, it is possible that the oils found in cranberry seeds are absorbed and could deliver medicinal benefits. However, in this regard, more work specifically on cranberry is needed.

Effects of Cranberry on Urinary Tract Infections and Urinary Tract Health

Consumption of cranberries and cranberry products has been widely recommended for the maintenance of urinary tract health in general (Bone and Morgan 1999; Henig and Leahy 2000; Kerr 1999; Patel and Daniels 2000; Reid, 1999; Wang et al. 2012b), as well as for the prevention and prophylactic treatment of urinary tract infections (UTIs) (Bonetta and Di Pierro 2012; Haverkorn and Mandigers 1994; Hess et al. 2008; Rogers 1991; Stothers 2002; Walker et al. 1997, among others). There are an almost equal number of studies with comparable numbers of subjects that report positive and negative outcomes. A variety of preparations have been used in the various studies including cranberry juice, cranberry juice cocktail (~27% juice), and varying cranberry extracts (see review of select studies below and Table 12). Some studies do not fully characterize the preparations used, while other studies report low compliance and high dropout rates (see Jepson et al. 2012). Patients with recurrent

UTIs appear to prefer "natural" therapies such as cranberry in order to avoid prophylactic antibiotic use (Mazokopakis et al. 2009; Nowack and Schmitt 2008) underscoring the importance for health care providers to understand the benefits, limitations, dosage, and product characterizations to maximize the efficacy of cranberry preparations. The most common dose used in early studies was approximately 300 mL of cranberry juice cocktail that, when calculated, delivers approximately 36 mg of soluble PACs (analyzed according to DMAC with an A2 standard). A variety of mechanisms for cranberry's putative effects have been articulated. For many years, it was assumed that hippuric acid excreted in the urine following cranberry consumption was responsible for the effect on prevention of UTIs as hippuric acid can be bacteriostatic against *E. coli* (at concentrations of 1–2 mg/L; Bodel et al. 1959; Hamilton-Miller 1976). In human trials, urinary pH levels were somewhat reduced following consumption of cranberry juice, but to achieve a bacteriostatic effect, urinary pH must be reduced to at least 5.0 with a minimum hippuric acid concentration of 0.02 M (Bodel et al. 1959; Blatherwick 1914; Blatherwick and Long 1923; Jackson and Hicks 1997; Kinney and Blount 1979; Nickey 1975; Papas et al. 1966; Schultz 1984a; Schultz 1984b). To attain these levels, humans would need to consume at least 1500 mL of cranberry juice per day (Kahn et al. 1967). To date, researchers have not yet elucidated an exact in vivo mechanism of action, although there is substantial in vitro and ex vivo evidence indicating that cranberry and cranberry A-type PACs stimulate an activity that results in inhibiting bacteria, particularly *E. coli*, from adhering to uroepithelial cells (Gupta et al. 2007; Howell et al. 1998; Sobota 1984; Zafriri et al. 1989), prevent formation of bacterial biofilms (LaPlante et al. 2012), hinder motility, and downregulate the enzyme urease and the transcription of flagellin, which are important virulence factors (McCall et al. 2013). In addition to other potentially bioactive compounds, cranberries contain a rich and diverse mixture of polyphenolic compounds. More research is needed to determine if and how these compounds contribute to the antiadhesion effect and modulate other systems to help prevent UTIs, such as through the immune system or by reducing uropathogenic bacteria invasion in the GI tract (Feliciano et al. 2014). It is likely that a suite of compounds contributes to cranberry's biological activity. More recently, focus has been given to PACs as the primary compounds with clinically relevant antiadherence activity. Preliminary in vitro data suggest phenolics may have a role to play (Gonzalez de Llano et al. 2015) but requires confirmation.

Live bacteria must attach and gain entry to uroepithelial cells in the urinary tract to grow and cause infection, and they do so by binding to certain cell receptors with filamentous appendages called pili or fimbriae. The antiadhesion activity of cranberry was first recognized by Sobota (1984). A series of experiments using cranberry juice and uropathogenic strains of *E. coli* demonstrated that cranberry juice contains one or more compounds that inhibit in vitro bacterial adherence to uroepithelial cells (Howell et al. 1998; Zafriri et al. 1989). It appears that by preventing the *E. coli* from adhering to uroepithelial cells, the bacteria will not grow and cause infection, but be flushed out in the urine stream. Since this mechanism is not killing the bacteria, it is unlikely to result in bacterial resistance to cranberry. Antiadhesion activity of cranberry has been demonstrated in humans (Di Martino et al. 2006; Howell et al. 2005; Howell et al. 2010; Lavigne et al. 2008; Tempera et al. 2010; Valentova et al. 2007).

Human Intervention Trials

UTIs are the most common bacterial infection in the ambulatory setting in the United States (Schappert and Rechtsteiner 2011). Although both males and females can develop a UTI, infections occur more frequently in women (Foxman and Brown 2003). It is estimated that more than 50% of women will experience at least one UTI in their lifetime (Griebling 2005), and 20 to 30% of women who experience a UTI will have 2 or more recurrent episodes (Foxman 1990). Other populations at higher risk for developing UTIs include children, pregnant women, the elderly, patients with spinal cord injuries, catheterized patients and those with chronic and/or immune-compromising diseases such as diabetes and HIV/AIDS (Foxman 2002). Foxman et al. (2015), found that administration of the equivalent of two 8-oz servings of cranberry daily in solid dosage form (capsule; TheraCran, Theralogix, LLC, Rockville, MD) for 6 weeks significantly (P =0.008) reduced the incidence of UTIs in post-surgical catheterized subjects (n = 160) by approximately 50% as compared to placebo controls. Subjects in this study were instructed to take the capsules morning and evening with an 8-oz glass of water beginning at time of discharge, and were specifically asked to avoid any other cranberry product or vitamin C supplementation for the duration of 4 to 6 weeks, or until their post-operative visit. There were no differences in adverse effects, including GI upset in this study.

A recent review of clinical studies (Micali et al. 2014) and evaluation of the cranberry efficacy/safety ratio in the prevention of UTIs supports the use of cranberry in the prevention of recurrent UTIs in young and middle-aged women (see Afshar et al. 2012; Ferrara et al. 2009; Kontiokari et al. 2001; Salo et al. 2012; Stothers 2002; Uberos et al. 2012; Walker et al. 1997; Table 12). However, evidence of its clinical efficacy among other groups remains controversial (Micali et al. 2014). Past clinical reviews have been mixed with several suggesting that cranberry may help prevent infections, particularly in women with recurrent UTIs (Jepson and Craig 2008; Wang et al. 2012b), with one review finding no benefit for cranberry (Jepson et al. 2012). Risk ratios of <1.0 (calculated relative risk of developing UTIs in the treated vs control groups) were interpreted as positive outcomes by Wang et al. (2012b) but not by Jepson et al. (2012) with different confidence intervals reported in each study. Compliance in some studies included in the Cochrane Review (Jepson et al. 2012) was low, but may have been confounded by the use of poor compliance measures. Most of the studies used cranberry products that were not standardized to A-type PACs and may not have

had sufficient amounts of bioactive PAC to achieve clinical efficacy. It is important to note that cranberry is a food that comes in different product forms (juice, powder, dried, etc.) making it difficult to use a meta-analysis to compare results from multiple trials that each used different product forms (Howell 2013). Additionally, the choice of study subjects is particularly important, as the pathogenesis of UTI is specific to different patient groups. Several studies completed since the Cochrane Review (Jepson et al. 2012) had positive outcomes for cranberry in preventing UTI recurrence and are included in the most recent review of Micali et al. (2014). However, more work is needed to determine the optimal dose, frequency of administration, length of consumption, subject characteristics, and product form.

Importantly, the Cochrane Review (Jepson et al. 2012) concluded that in studies comparing low-dose antibiotics to cranberry for UTI prevention, there was little difference between cranberry and antibiotic prophylaxes, with both being similarly effective. In fact, in a study conducted by Beerepoot et al. (2011), antibiotic prophylaxis resulted in trimethoprim-sulfamethoxazole (TMP-SMX) resistance in 86.3% of fecal and 90.5% of asymptomatic bacteriuria *E. coli* isolates after one month on low-dose TMP-SMX, while in the cranberry group (1000 mg CranMax®; Pharmachem Labs; Kearny, NJ, 23.7% of fecal and 28.1% of asymptomatic bacteriuria *E. coli* isolates were TMP-SMX resistant. These same researchers also found increased resistance rates for trimethoprim, amoxicillin, and ciprofloxacin in these *E. coli* isolates after one month in the TMP-SMX group (see Interactions). Due to the very low risk of resistant bacterial strain development, cranberry was recommended by these study authors as a viable alternative to low-dose antibiotics to prevent UTI. Since the increasing prevalence of *E. coli* resistance to first-line antimicrobials in the treatment of acute UTI in women is also a serious problem (Stapleton 2013), use of cranberry to prevent initial infections may help reduce the need for subsequent antibiotic treatments and slow the pace of resistance development. According to the World Health Organization (WHO 2014) Antimicrobial Resistance Global Report on Surveillance, resistance to fluoroquinolones for controlling UTIs is very widespread, and compared with the 1980's, resistance rates have gone from 0 to 100% in many parts of the world. Cranberry products, therefore, may be a prudent nutritional therapy that can help maintain urinary tract health (Blumberg et al. 2013).

A pilot study by Greenberg et al. (2005) (n = 5) suggested that consumption of a single serving of sweetened dried cranberries (Craisins® Ocean Spray) may elicit bacterial antiadhesion activity in human urine and may be a healthy snack with specific genitourinary benefits.

Cranberry and Urinary Tract Health in the Elderly

One of the earliest large, double-blind, placebo-controlled randomized clinical trials evaluated a low calorie 27% cranberry juice cocktail for its effect on bacteriuria (defined as $>10^5$ cfu/mL of urine) and pyuria (white blood cells in urine) in 153 elderly women over a 6-month period (Avorn et al. 1994). Participants consumed either 300 mL/day of cranberry juice cocktail or 300 mL/day of a placebo drink. After 48 weeks of treatment, bacteriuria and pyuria were reduced by nearly 50% in the group that consumed cranberry juice cocktail with their odds of remaining bacteriuric-pyuric at only 27% of the odds of the control group (P =0.006). In another study (randomized, controlled, crossover), Haverkorn and Mandigers (1994) administered 30 mL/day of cranberry juice diluted in water to 17 elderly men and women for 4 weeks. Participants consuming the cranberry treatment had fewer occurrences of bacteriuria compared to those who drank water (P =0.004), confirming Avorn's findings that cranberry juice consumption reduces frequency of bacteriuria in the elderly. An uncontrolled study of 28 elderly patients in a long-term care facility found that cranberry juice was effective in preventing UTIs (Gibson et al. 1991). Participants drank 120 to 180 mL of cranberry juice cocktail almost daily for 7 weeks. UTIs were prevented in 19 of the 28 participants. A retrospective cross-sectional study and a longitudinal cohort study (Dignam et al. 1998) were carried out in a long-term care facility in which there was a 20-month pre-intervention period when UTI rates were recorded, and an 8-month intervention period when cranberry juice or cranberry capsules were given to participants (only 4% received the capsules instead of the juice). The cross-sectional study involved 538 elderly people (77% women and 23% men). During the 20-month pre-intervention period, UTIs were reduced significantly between these 2 periods (P =0.008), with 545 UTIs compared with 164 UTIs during the 8-month intervention period when cranberry juice was consumed. In the longitudinal cohort study, 113 residents participated. There were 103 UTIs during the pre-intervention period and 84 UTIs during the intervention period, which represented a trend toward reduction in UTIs.

A double-blind, randomized, placebo-controlled pilot study aimed at identifying the optimal dose of cranberry capsules needed to reduce the incidence of bacteriuria plus pyuria was conducted over a 1-month period in elderly nursing home patients (Bianco et al. 2012). Subjects (n = 80) were given either 3 cranberry capsules (108 mg PAC determined by DMAC assay); 2 cranberry capsules (72 mg PAC) plus one placebo; or one cranberry capsule (36 mg PAC) plus 2 placebos; or 3 placebo capsules for 30 days, measuring episodes of bacteriuria and pyuria at days 7, 14, 21, and 28. In those consuming cranberry, a dose-dependent trend towards a reduction in bacteriuria and pyuria (particularly with *E. coli*) was observed, most notably in women. Cranberry did not affect bacteriuria with pathogens other than *E. coli*. The effects of the 2-capsule dose were comparable to those of the 3 capsule dose. Neither the long-term sustainability of the reduction in bacteriuria and pyuria, nor effects on clinical outcomes related to UTI (e.g., hospitalization, antibiotic therapy) was determined.

A double-blind, randomized placebo-controlled multicenter trial (n = 928) was conducted to determine the efficacy of cranberry (undisclosed characterization and dose taken twice daily for 12 months) in reducing the incidence of UTIs in residents of long-term care facilities (703

women, median age 84 years) in the Netherlands (Caljouw et al. 2014). Subjects were stratified by low or high UTI-risk (including long-term catheterization, diabetes mellitus, and ≥1 UTI in the preceding year). Of the total subjects, 516 were stratified as having a high risk for UTI; 412 were considered low risk. Compared to placebo, a 26% reduction in UTI was observed in the high-risk group, while no difference was observed in the low-risk group. One limitation of this study is that the actual incidence of UTIs was lower in the cranberry compared to placebo group.

In a recent study by Barnoi et al. (2015), prophylactic administration of 120 mg cranberry (preparation not characterized) daily significantly reduced the incidence of UTI as compared to a control group of patients with in-dwelling catheters (12.9% versus 38.75%, respectively; $n = 31$ in treatment and control groups; $P = 0.04$).

Cranberry in Women with Recurrent UTIs

Cranberry products have been evaluated in 5 clinical trials to determine their efficacy in preventing recurrent UTIs in women. Three of the trials had a successful primary outcome regarding cranberry consumption and the prevention of recurrent UTIs (Kontiokari et al. 2001; Stothers 2002; Walker et al. 1997), while the other studies did not demonstrate a significant effect (Barbosa-Cesnik et al. 2011; Stapleton et al. 2012). Only 3 trials were randomized, double-blind, placebo-controlled (Barbosa-Cesnik et al. 2011; Stapleton et al. 2012; Walker et al. 1997), but none was adequately powered statistically. All trials recruited healthy women, ages 18 to 72 years, with a history of at least one UTI within the previous year. Cranberry regimens and dosing varied greatly among these studies. Walker et al. (1997) provided participants with 400 mg of encapsulated cranberry solids taken once per day for 3 months. Kontiokari et al. (2001) used cranberry-lingonberry juice made from concentrates, primarily containing cranberry: 7.5 g cranberry concentrate and 1.7 g lingonberry concentrate diluted in 50 mL water once daily for 6 months. Kontiokari et al. (2001) also compared 100 mL of a probiotic milk drink containing *Lactobacillus* for 5 days/wk for one year to 150 women who were recruited with UTIs; an open group served as open controls. After 6 months, the women on the cranberry treatment experienced 56% fewer UTIs (defined as $>10^5$ cfu/mL) than the control group ($P = 0.02$). After 12 months, the cumulative occurrence of the first episode of UTI was still significantly different between the groups ($P = 0.048$), suggesting that cranberry juice drink was effective in preventing UTI, while the probiotic drink was not. The Stothers (2002) study had 2 cranberry treatment arms, administered as a juice or tablet. Participants in the juice arm consumed 250 mL of "pure, unsweetened" cranberry juice 3 times/day, and the tablet arm received a 1:30 parts concentrated cranberry juice tablet twice per day for 12 months. A double-blind, placebo-controlled, crossover study by Walker et al. (1997) found that dried cranberry powder was effective in reducing UTI occurrence. Women between the ages of 28 and 44 with a history of recurrent UTIs were recruited to take two 400-mg cranberry extract pills per day for 3 months (and 3 months of placebo). While taking cranberry pills, 7 out of the 10 women experienced fewer UTIs. Only 6 UTIs occurred among the 10 subjects on cranberry supplementation, while 15 UTIs occurred among the 10 subjects on the placebo. The authors concluded that cranberry extract pills were more effective than placebo in reducing UTI occurrences ($P < 0.005$). Participants in the Barbosa-Cesnik et al. (2011) study consumed two 240 mL cranberry beverage per day for 6 months; these subjects entered the trial with acute UTIs. Participants in the study of Stapleton et al. (2012) consumed the same juice beverage, assigned to one 120 mL/day or 240 mL/day for 6 months. Papas et al. (1966) conducted an uncontrolled study in which 480 mL/day of cranberry juice cocktail was administered for 21 days to 60 patients (44 women and 16 men) diagnosed with acute UTI. After 3 weeks, 53% of the participants experienced fewer UTIs following cranberry juice consumption. Six weeks after discontinuation of cranberry treatment, bacteriuria returned in most subjects. Each study reported total PAC concentration but used different methods to quantify PACs, thus giving inaccurate and varied results that are inconsistent with current quantification methods.

A recent study in which women with recurrent UTI were given 42 g dried cranberries/day for 2 weeks followed by observations for 6 months showed that women taking dried cranberries had significantly lower incidence of UTI, with a mean UTI rate at 6 months decreasing from 2.4 to 1.1 compared to a historical control group enrolled in a previous vaccine control study (Burleigh et al. 2013). Those women in the dried cranberry group also had a significant reduction in *E. coli* in a rectal swab taken post-consumption. Recently, Takahashi et al. (2013), provided 125 mL/day of cranberry juice (Group A) compared with placebo (Group P) for 24 weeks to women between 20 to 79 years with recurrent UTI. In the subgroup of females aged 50 years or more, there was a significant difference in the rate of relapse of UTI between groups A and P (log-rank test; $P = 0.0425$). A study by Sengupta et al. (2011) found symptomatic relief and significant reduction ($P < 0.05$) in the subjects positive for *E. coli* in both the high dose (1000 mg) and low dose (500 mg) treatment groups given a standardized cranberry powder for 90 days, compared to baseline evaluation in a randomized clinical trial of 60 female subjects between 18 to 40 years of age.

In a recent randomized placebo-controlled trial, 164 women with a history of at least 2 symptomatic UTIs in the previous 12 months, were given 500 mg of "whole cranberry fruit powder" consisting of the "peel, seeds, and pulp" (Naturex-DBS, Sagamore, MA) delivering 2.8 mg PACs daily (determined by DMAC using the A2 standard) for 6 months. There were 78 women in the treatment group and 86 in the placebo group. Consistent with numerous other individual trials, there were significantly fewer recurrent UTIs in the treatment versus placebo groups (10.8% vs. 25.8%, respectively, $P = 0.04$). The authors reported there were no anthocyanins or PACs detected in plasma or urine, no significant differences in urinary phenolics between the groups, and speculated that PACs were not correlated with

the effects, rather suggesting that other compounds, such as ursolic acid, may play a role (Vostalova et al. 2015). This is the first such trial demonstrating the efficacy of a whole cranberry powder.

Cranberry and Recurrent UTIs in Pregnancy

Asymptomatic bacteriuria, defined as $>10^5$ CFUs/mL of uropathogenic bacteria in the urine, without the traditional symptoms associated with UTIs, is of particular concern in pregnant women due to their association with pre-term delivery and low birth weight (Romero et al. 1989; Sheiner et al. 2009). Untreated, asymptomatic bacteriuria in pregnancy may progress to a UTI, particularly pyelonephritis (Kass 1960), which is associated with increased risk to both the neonate and the pregnant woman (Farkash et al. 2012).

The first study published to investigate the effect of cranberry on ASB/UTI in pregnant women did not find a statistical difference in asymptomatic bacteriuria, UTI, or neonatal outcomes among participants who were compliant with zero, one, or two 8 oz. servings of a cranberry beverage per day. The beverage treatments were reduced to 2 servings per day (Wing et al. 2008), and although this study was underpowered, women compliant with two 8 oz servings of cranberry per day experienced a 57% reduction in asymptomatic bacteriuria and 41% reduction in UTIs, indicating that cranberry may be efficacious in preventing asymptomatic bacteriuria and UTIs in pregnant women. Further studies would help solidify this area of importance for pregnant women and UTI prevention. A recent literature review of pregnant women taking cranberry supplement compared with antibiotics showed no adverse effects on the mother or infants including no increased risk of malformations nor any of the following pregnancy outcomes: stillbirth/neonatal death, preterm delivery, low birth weight, small for gestational age, low Apgar score, and neonatal infections, suggesting that cranberry consumption during pregnancy has no safety concern (Heitmann et al. 2013). Although an association was found between use of cranberry in late pregnancy and vaginal bleeding after pregnancy week 17, further sub-analyses of more severe bleeding outcomes did not support a significant risk (see Precautions and Safety). This review provided no characterization of the products or doses utilized and are juxtaposed against one formal study (Wing et al. 2008) and other reviews (Nordeng et al. 2011) showing no such effect.

Recurrent UTIs in Children

Recent trials in the pediatric population have demonstrated a benefit from cranberry consumption. The 5 available trials used a variety of cranberry products: 7.5 g cranberry concentrate plus 1.7 g of lingonberry concentrate diluted in 50 mL of water per day for 6 months (Ferrara et al. 2009); commercially available cranberry juice containing 8.2 g of cranberry concentrate per 200 mL water administered at 5 mL/kg body weight per day for 6 months (Salo et al. 2012) a cranberry syrup containing 36 mg PAC (Ellura®/Urell®; Pharmatoka Labs, Rueil-Malmaison, France) measured by DMAC with A2 reference standard) administered at 5 mL per day depending on body weight (Uberos et al. 2012); and cranberry juice containing 37% PACs (PAC quantitation not specified) administered at 2 mL/kg body weight for one year (Afshar et al. 2012). The primary outcomes analyzed demonstrated that cranberry treatment was efficacious in reducing UTI risk by 65% (Afshar et al. 2012) and preventing UTI recurrences (Ferrara et al. 2009). The primary outcome of reducing the number of children who experienced a recurrent UTI was not statistically significant in the Salo et al. (2012) trial. Cranberry treatment did, however, significantly reduce the number of recurrent UTIs and the number of days on antibiotics. In the trial of Uberos et al. (2012), cranberry prophylaxis was safe and effective having non-inferiority with respect to trimethoprim in recurrent UTI in relation to vesico-urethral reflux in 192 children ages 1 month to 13 years. In a follow-up analysis of their work (Uberos et al. 2015), the authors reported cranberry intake was correlated with high levels of hydroxycinnamic and hydroxybenzoic acids in urine and suggested these metabolites may play a therapeutic role in the UTI preventive effects of cranberry in vivo. One group of subjects was given a 3% glucose solution of cranberry extract (Urell®, Pharmatoka Labs, Rueil-Malmaison, France) yielding 4732 µg/mL of PACs at a dose equivalence of 5.6 mg/kg of extract; the other group was given trimethoprim in a similar syrup base at a concentration of 8 mg/mL and 0.1% CC-1000-WS (E-120) at a dose of 1.6 mg/kg. Subjects included 85 children less than 1 year of age, 53 of whom were treated with trimethoprim and 32 with cranberry syrup and 107 children over 1 year of age, 64 of whom were treated with trimethoprim and 43 with cranberry syrup. There were marked differences in efficacy in children under one year of age and those over, as well as between treatment groups. In the trimethoprim group, rates of UTI in males and females under one year of age were 19% and 43%, respectively. Interestingly, gender associated efficacy was reversed in the cranberry group, the UTI rates in male and female children under one year of age being 46% and 17%, respectively. When adjusting for gender differences, in those under one year of age, the overall rates of UTI recurrence in the trimethoprim group was 28% and in the cranberry group 35%. Similarly, a reversal of the rate of efficacy was observed in children over one year of age, the UTI rate being 35% in the trimethoprim group and 26% in the cranberry group. These researchers concluded that overall, cranberry syrup was similar in efficacy and safety to trimethoprim, but that in children under one year of age trimethoprim was more effective than cranberry syrup. Conversely, cranberry was slightly more effective than trimethoprim in reducing the incidence of multi-resistant bacteria in urine culture, with 22.9% of the cranberry group displaying positive cultures compared to 33.3% in the trimethoprim group.

A recent meta-analysis of the use of cranberry in the prevention of UTIs in children concluded that cranberry products are effective in otherwise healthy children and at least as effective as antibiotics in children with urogenital abnormalities. A dosage and frequency recommendation is confounded by the variability of products and dosages used

in the trials included in this analysis (Durham et al. 2015).

Cranberry and Urinary Tract Health in Neurogenic Bladder and Spinal Cord Injury

Neurogenic bladder is the result of problems with nerves in the body that control how the bladder stores and empties urine. Results of intervention trials using cranberry juice for UTI prevention in patients with neurogenic bladders are not clear. One double-blind, placebo-controlled, crossover study did not find a significant reduction in bacteriuria in children ages 2 to 18 years with neurogenic bladders after 60 mL/day cranberry juice concentrate consumption (Schlager et al. 1999) (equal to 300 mL/day of cranberry juice cocktail) or a placebo for 3 months with another 3-month crossover. The authors suggest that the voiding dysfunction associated with neurogenic bladder may have overshadowed the effect of cranberry in this population. In a crossover study by Foda et al. (1995), cranberry juice consumption did not significantly reduce UTIs in a pediatric population with neurogenic bladders. Participants (n =21) consumed either 15 mL/kg/day of body weight/day of cranberry juice cocktail or 15 mL/kg of body weight/day of water for 6 months, with a 6-month crossover. There was no significant difference in UTI reduction between cranberry juice consumption and water consumption in this group of participants. However, in an uncontrolled study, Rogers (1991) administered 360 to 480 mL/day of cranberry juice to 17 children with neuropathic bladders for one week and 540 to 660 mL/day during the second week. All urine samples had reduced red and white cell counts, suggesting reductions in UTIs following cranberry consumption.

The evidence for effectiveness of cranberry supplementation on UTI prevention and bacteriuria in spinal cord-injured individuals is inconclusive. Two studies found no reduction in bacteriuria or pyuria with cranberry supplementation (Linsenmeyer et al. 2004; Waites et al. 2004), and one study did not result in a longer UTI-free period on cranberry compared to placebo (Lee et al. 2007). However, a crossover, double blind, randomized, placebo-controlled trial of 47 subjects with spinal cord injury and neurogenic bladder did find a reduction in symptoms and a 60% reduction both in the number of UTI and of subjects who experienced any UTI over a 6-month trial in those subjects receiving a daily 500-mg cranberry tablet taken twice per day compared to placebo. Subjects taking cranberry did not experience a reduction in urinary pH. UTI was nearly eliminated among subjects in the cranberry group with a glomerular filtration rate (GFR) above 75 mL/min–1. The authors hypothesized that the combination of bacterial adhesion inhibition and a high urinary filtration rate worked together to prevent bacterial biofilm formation and eliminate the bacterial pathogens (Hess et al. 2008). Bacterial biofilm load was significantly reduced in a study of 15 spinal cord-injured participants who consumed 3 glasses of cranberry juice on days 7 and 15 compared to those that consumed 3 glasses of water on those days. The results in the cranberry group were due to a reduction of both gram-negative and gram-positive bacterial adhesion to cells (Reid et al. 2001). These findings suggest that different risk factors or populations studied may contribute to some of the inconsistent results found with cranberry prophylaxis. However, a nutritional approach utilizing cranberry to reduce the incidence of UTIs has significance due to the potential for reducing antibiotic treatment and the consequent development of resistance to these drugs (Blumberg et al. 2013).

Other Urinary Tract Effects

Administration of a daily cranberry encapsulated powder containing 36 mg PAC, as measured by DMAC with the A2 standard significantly decreased asymptomatic bacteriuria in patients with an ileal enterocystoplasty (bladder replacement) (Botto and Neuzillet 2010). There have been several clinical reports of cranberry juice having a beneficial effect on reducing catheter-obstructed mucus production in enterourocytoplasties (Rosenbaum et al. 1989) and in catheterized children (Rogers 1991), as well as reducing urine odor (DuGan and Cardaciotto 1966; Kraemer 1964). *E. coli* alkalinizes and ferments the urine with a subsequent release of ammonia. Cranberry juice lowered urinary pH sufficiently (from 6.6 to 5.8) to retard this bacterial action and reduce the ammonia smell (Kraemer 1964). DuGan and Cardaciotto (1966) found that ammonia odor and burning sensation while urinating were reduced following administration of 90 mL/day for one week, with a weekly increase of 30 mL/day until a maximum dosage of 180 mL/day was reached after 3 weeks. Ammonia odor was actually measured in the air and was reduced, especially in the female group, after the intervention period. Conversely, no beneficial effect was observed in in-home subjects (n = 11) with in-dwelling catheters (Lin et al. 2014). In this study, no significant differences were observed on urinalysis, urine culture, and biochemical blood tests compared to controls. Subjects consumed 300 mL cranberry juice cocktail and 2200 mL of water.

There is mixed evidence on the effects of cranberry juice consumption and kidney stone formation stones with some reporting a risk a potential but slight increased risk of stone formation (e.g. Gettman et al. 2005) and others reporting decreased risk (Light et al. 1973; Zinsser et al. 1968). Most of these opinions are based on biomarkers of stone formation rather than clinical outcomes showing an increase or decrease in stones. Findings on all biomarkers used have been mixed with reports of urinary calcium excretion increasing, decreasing, or remaining unchanged; urinary oxalate excretion to decrease or increase; and urinary citrate to increase or remain unchanged with consumption of cranberry juice (see Gettman et al. 2005). These variations are likely due to differences in the preparations consumed.

Regarding calcium oxalate stones, concerns have been raised about high intakes (1 L or more/day) of cranberry juice due to the potential of oxalate and uric acid stones forming in acidic urine (Rogers 1991). In one early investigation, cranberry juice consumption of up to 2.4 L/day significantly reduced urinary ionized calcium associated with calcium-containing renal stones by 50% (P =0.001) (Light et al. 1973). Further more, Brinkley et al. (1981) reported

that cranberry juice contained low or negligible amounts of oxalate and was safe for patients with calcium kidney stones. In contrast, Gettman et al. (2005; see *Association between cranberry consumption and increased kidney stone formation* below) reported that cranberry juice consumption increases the risk of calcium oxalate and uric acid stone formation but decreases the risk of brushite stones. These authors also concluded that cranberry juice CBJ "probably does not substantially affect the risk of stone formation. Similarly, Terris et al. (2001) reported a potential increase in oxalate stone formation based on increases in urinary excretion of calcium, sodium, and phosphate, lithogenic ions, in normal volunteers, though increases in magnesium and potassium, antilithogenic ions, was also observed.

Regarding struvite stones, bacteria in the urine can alkalinize and facilitate the formation of struvite calculi (Zinsser et al. 1968). In another early study, patients (53) who consumed 946 mL/day of cranberry juice over 9 years reportedly had a 60% improvement with no stone formation, 32% had no increase in stone size, and 8% had new stones form or an increase in stone size (Zinsser et al. 1968). This effect was assumed to be due to urinary acidification by cranberry juice but could have been associated with decreases in stone formation due to urinary tract infection (Light et al. 1973).

In a recent investigation, Rafsanjany et al. (2015) investigated the in vitro, in vivo, and ex vivo antiadhesin activity of cranberry extracts, one enriched and the other devoid of PACs. Four males were given 600 mg of a cranberry extract containing 1.24% PACs (as determined by LC-MS and calculated as cyanidin), and another devoid of PACs (as determined by TLC), for seven days. Urine samples were taken at days 0, 3, and 7 and antiadhesin assays were conducted. Significant (P <0.01) reductions in bacterial adhesion were reported at days 3 (-39%) and 5 (-48%) compared to the control (day 0) for both cranberry preparations. This investigation confirms earlier in vitro findings (e.g., see Feliciano et al. 2013) that high PAC extracts can result in a clumping (agglutination) of bacteria on the surface of bladder cells and that non-PAC preparations also selectively inhibit bacterial adhesion (e.g., Type 1 *E. coli*; Hotchkiss et al. 2015; Zafriri et al. 1989). These researchers cautiously interpret that part of the in vitro bacterial antiadhesion activity of cranberry is due to tannin-induced agglomeration, a novel theory. These investigators further confirm that PACs inhibit bacterial adhesion to urinary bladder cells but emphasize that PAC metabolites (e.g., catechol, myricetin, phenylacetic acid, 3,4-dihydroxyphenylacetic acid,) may have a greater role in bacterial antiadhesion activity than previously reported (Kimble et al. 2014; de Llano et al. 2015). Other research similarly confirms that compounds in addition to PACs exhibit antiadhesin activity (see Hotchkiss et al. 2015; Zafriri et al. 1989). In the study of Rafsanjany et al. (2015), neither the PAC extract nor the PAC-depleted extract influenced biofilm or curli development. In contrast to the findings of other studies, these investigators also reported that P-fimbriae-mediated adhesion was not influenced by these cranberry preparations.

In Vitro, Ex Vivo, and Animal Studies

Bacterial Antiadhesion and Other Potential Mechanisms

The results of in vitro studies on cranberry indicate there may be multiple mechanisms contributing to the fruit's beneficial effects, with a significant number of investigations focusing on bacterial antiadhesion. There are many in vitro and ex vivo studies on cranberry, cranberry products, and isolated cranberry A-type PACs demonstrating significant antiadhesion effects on mainly *E. coli* bacteria. There are 2 major uropathogenic *E. coli* fimbrial types, P-type (or pyelonephritis-associated pili [PAP]), which are mannose-resistant, and Type 1, which are mannose-sensitive. The bacterial antiadhesion effect of cranberry targets P-fimbriated *E. coli* (Sobota 1984), which are associated with both cystitis and pyelonephritis (Dowling et al. 1987).

There are different types of cranberry compounds that have been implicated in the antiadhesion effect: fructose and high molecular weight compounds identified as A-type PACs (Howell et al. 1998; Zafriri et al. 1989) and phenolic compounds. Binding studies demonstrate that fructose has a high affinity to the Type 1 FimH adhesin, although 15-fold less than its natural mannose ligand (Bouckaert et al. 2005). Incomplete metabolism of fructose in the liver can lead to its urinary excretion, but is normally only clinically significant at very high sugar doses (Tasevska et al. 2005) or in diabetics (Kawasaki et al. 2002). Thus it is unlikely that the fructose in cranberry elicits a significant in vivo antiadhesion effect in most people. The majority of research has focused on the A-type PACs as the key compounds responsible for preventing adhesion of P-type *E. coli* (Ermel et al. 2012; Foo et al. 2000a, 2000b; Howell et al. 2005; Howell 2007). Recently, Gupta et al. (2012) showed cranberry PAC extracted from dried juice prevented the in vitro binding of both sensitive and multi-drug resistant P-fimbriated *E. coli* at concentrations of 10 to 50 µg/mL/day. Purified cranberry PACs fed to mice for 20 days at 0.122 or 0.522 mg/day in water elicited significant bacterial antiadhesion activity in urine when compared to the urine collected from control mice that were consuming plain water (P <0.01) (Howell et al. 2001).

In another animal study, urine from rats fed 118 mg PACs/animal/day in oral suspension form or tablets prevented adhesion of *E. coli* by 83% and 52%, respectively (Risco et al. 2010). PACs appear to prevent bacterial adhesion in multiple ways, including causing morphological changes in the bacteria such as elongation or fimbrial compression, preventing binding to uroepithelial cells (Ahuja et al. 1998; Liu et al. 2006). In another animal study, rats were administered 1 mL of either diluted (25%) or pure cranberry juice three times daily. Significant decreases in *E. coli* hemagglutination, urothelium adhesion, and biofilm formation along with significant increases in nematode killing were observed with both cranberry preparations. There was greater activity of the pure juice over the diluted cranberry juice preparation (Chen et al. 2013).

In a study of Gonzalez de Llano et al. (2015), a variety of phenolic compounds and their metabolites (catechol, benzoic acid, vanillic acid, phenylacetic acid, and 3,4-dihydroxyphenylacetic acid; 100 to 500 µM) showed in vitro

antiadhesion activity against *E. coli* in uroepithelial cells. According to the authors this is the first time antiadhesion activity was demonstrated for these compounds. However, these phenolics are also metabolites of A-type PACs so such an activity is not surprising. Additionally, the authors acknowledge that in vivo relevance has not been established. The study also confirmed the antiadherence activity of PACs (500 µM).

A group of researchers used atomic force microscopy to elucidate the effects of cranberry products on the ability of bacteria to attach to uroepithelial cells (Liu et al. 2006; 2010). In initial studies, the researchers found that the cranberry products decreased the attachment of *E. coli* HB101pDC1, a fimbriated strain, but not *E. coli* HB101, a non-fimbriated strain (Liu et al. 2006). Later they found that bacterial exposure to increasing concentrations of cranberry juice cocktail (27% cranberry by weight) or incubation in isolated cranberry PAC (345.8 µg/mL/day) resulted in a decrease of bacterial attachment to uroepithelial cells for the P-fimbriated strain (Pinzon-Arango et al. 2011).

Results of in vitro studies are helpful in determining mechanisms and potency of products prior to ingestion; but, to more accurately determine efficacious dosages and persistence of cranberry, studies using hemagglutination or bladder cell adhesion assays that measure the ex vivo urinary antiadhesion activity following consumption are important. Sobota (1984) found that urine collected from mice that ingested cranberry juice cocktail in place of water for 14 days significantly inhibited adherence of P-fimbriated *E. coli* to uroepithelial cells ($P < 0.01$). This antiadhesion effect was also detected in human urine in 15 of the 22 subjects, 1 to 3 hours following ingestion of 450 mL of cranberry juice cocktail (Sobota 1984). Since then, other studies have also found ex vivo bacterial antiadhesion activity in human urine following cranberry consumption (Di Martino et al. 2006; Howell et al. 2010; Tempera et al. 2010; Valentova et al. 2007). Lavigne et al. (2008) found that urine from subjects consuming 3 capsules of cranberry preparation caused a highly significant reduction in bacterial adherence to T24 cells as compared with placebo ($P < 0.001$) with a dose-dependent decrease in bacterial adherence. The ex vivo antiadhesion activity in urine was also demonstrated following ingestion of different dosages of cranberry juice powder standardized for PAC content (Howell et al. 2010). Dosages of cranberry powder containing 36 or 72 mg PAC levels/day as measured by DMAC method with a procyanidin A2 reference standard (Prior et al. 2010a) elicited significantly higher antiadhesion activity in urine using both the hemagglutination and human T24 epithelial cell line bioassays at 6 hours than powder dosages containing 18 mg of PAC ($P = 0.002$) (Howell et al. 2010).

Biofilms are typically associated with catheter-associated UTIs, but have recently been implicated in the etiology of recurrent UTI (Anderson et al. 2004). Biofilms, sessile communities of bacteria, form an extracellular matrix for functional and structural integrity and have altered phenotypes associated with long-term persistence (Dolan et al. 2010). Ex vivo biofilm studies have demonstrated that urine from cranberry juice consumers can prevent biofilm formation in uropathogenic *E. coli* (Camesano et al. 2011; Di Martino et al. 2005), implying that active compounds are present in the urine following cranberry consumption.

Flagellum-mediated motility has been suggested to enable uropathogenic *E. coli* to reach the upper urinary tract. It was proposed that inhibition of flagellum-mediated motility might be a key mechanism by which cranberry PACs prevent UTIs. The authors of a study using *E. coli* strain CFT073 grown in the presence of dehydrated crushed cranberries or purified cranberry PACs results in a reduction of fliC (flagellin gene) expression by almost 2.4-fold (Hidalgo et al. 2011). Additionally, the study showed that 0.1 to 10 mg/mL/day of cranberry PACs can slow or completely prevent swimming or swarming motility of the bacteria. Chan et al. (2013) reported a similar action of cranberry powder and cranberry PACs to downregulate the expression of the flagellin gene of *E. coli* CFT073 and Proteus mirabilis HI4320 in vitro in a silicone gel model. Interestingly, these researchers suggest the application of cranberry compounds into medical devices (e.g., catheters) as a way to reduce the migration of bacterial pathogens.

Additional research is needed to determine more specifics on cranberry and bacterial adhesion and other potential mechanisms of action in support of urinary tract health. Questions remain regarding the specific in vivo antiadhesion mechanism due to lack of both bioavailability of larger polymeric A-type PACs (which are prevalent in cranberry skins, thus limiting their solubility) and published ex vivo antiadhesion data from clinical trials.

Recently, A-type PAC dimers have been shown to be bioavailable in small concentrations (Zampariello et al. 2012) with maximal urinary concentrations of A2 PACs averaging 24.4 ng/mg creatinine at 11 hours post-cranberry consumption. There are very few studies that have focused on metabolism of A-type PACs (e.g., Iswaldi et al. 2013; Rajbhandari et al. 2011). This area needs further study to more clearly determine the quantity and size of A-type PAC molecules that enter the urine following metabolism (see Pharmacokinetics). It is clear that the antiadhesion effects are complex and multi-faceted. It is also possible that an antiadhesion response may be induced indirectly in the urine following gut binding of larger PACs, or that these larger PACs bind directly to uropathogenic rectal *E. coli*, preventing fimbrial adherence to uroepithelial receptors following introduction of these bacteria into the urinary tract. Gut colonization by extra-intestinal pathogenic *E. coli* serves as a source of bacteria for subsequent UTIs, thereby increasing recurrence risk. Cranberry A-type PACs have also been shown to inhibit invasion of these *E. coli* into gut cells, potentially reducing the reservoir of bacteria for future infections (Feliciano et al. 2014).

Summary

The accumulative in vivo data, including numerous positive clinical studies with almost 3,000 thousand subjects, along with strong mechanistic rationale, suggest efficacy of cranberry and its preparations for maintaining urinary tract

health and the potential to reduce UTIs. Conversely, an almost equal number of studies with more than 1600 subjects failed to show efficacy in UTI prophylaxis or treatment, perhaps partially due to the use of ineffective products or insufficient doses.

Efficacy of cranberry for urinary tract health is likely due to multiple effects that include antiadhesion activity, modulation of bacterial motility, bactericidal activity, immune modulation, and urine acidification. A-type PACs are predominantly associated with the antiadhesion activity, with suggestions that 36 mg of PACs daily (as determined by DMAC with the A2 reference standard) is the target dose. This 36-mg dose is the amount of PACs in a typical 300 mL serving of cranberry juice cocktail (27% juice) as determined by the DMAC method (A2 reference standard), which showed efficacy in prevention of bacteriuria in elderly women (Avorn et al. 1996). Another well-designed clinical trial established the efficacy of whole cranberry fruit (delivering 2.8 mg PACs daily) in reducing recurrent UTIs (Vostalova et al. 2015). Other mechanistic data suggest that phenolics, metabolites of A-type PACs, may play a greater role than previously believed (Gonzalez de Llano et al. 2015; Rafsanjany et al. 2015). Still additional data report on antiadhesin activity of xyloglucan oligosaccharides (Hotchkiss et al. 2015), further establishing that a suite of compounds contributes to the overall activity of cranberry. Efficacy has been demonstrated for a variety of preparations including dried fruit, cranberry juice, cranberry juice cocktail, cranberry juice extracts, solid extracts, and a syrup. An important aspect of cranberry as a nutritional approach in potential prevention of UTIs is in lessening the need for conventional antibiotic therapy that leads to resistant bacterial strains. With very rare exceptions, cranberry has been demonstrated to be safe in adults, children, the elderly, and in pregnancy.

As reflected in the findings of the latest Cochrane review (Jepson et al. 2012), more rigorous randomized controlled clinical trials are needed as all studies to date can be criticized for having some methodological flaws.

Effects on Cardiovascular Health Cranberry Polyphenols: Effects on Cardiovascular Risk Factors

A continually increasing body of scientific evidence supports a positive relationship between the dietary consumption of foods that are high in polyphenolic compounds (e.g., flavonoids, phenolics, anthocyanidins), compounds found in cranberry, and reduced risk factors for cardiovascular disease (see Blumberg et al. 2013; Cassidy et al. 2011; 2013; Jennings et al. 2012; Hooper et al. 2008; Khoo and Falk 2014; Krueger et al. 2014; McCullough et al. 2012; Mink et al. 2007; Wallace 2014). Health effects associated with cranberry compounds include the inhibition of low-density lipoprotein oxidation (oxLDL), platelet aggregation and adhesion (Basu et al. 2010; Basu and Lyons 2012), and inflammatory response of vascular tissues and increases in endothelium-dependent vasodilation, as well as reductions in arterial stiffness (Dohadwala et al. 2011; Jennings et al. 2012) and blood pressure (Cassidy et al. 2011; Jennings et al. 2012). Current research specifically supports the function of polyphenols in modulating signal transduction through direct action on receptors and enzymes, which in turn influence redox reactions in the body (Scalbert et al. 2005; Stevenson and Hurst 2007).

Most findings correlating polyphenol consumption with cardiovascular protective effects are drawn from epidemiological data and dietary surveys, as well as systematic reviews, most of which do not specifically include cranberry. Thus a direct extrapolation of such findings to cranberry cannot be made. However, specifically regarding cranberry, well-controlled clinical trials have emerged supporting the effects of cranberry polyphenols in modulating cardiovascular risk factors such as hypertension, dyslipidemia, C-reactive protein, and oxidative stress markers such as LDL oxidation. Specific cardio-related risk factors that have been favorably influenced by cranberry or its constituents include arterial stiffness, diabetes, dyslipidemia, endothelial dysfunction, hypertension, inflammation, oxidative stress, and platelet function, suggesting potential benefit in atherogenesis, lesion progression, myocardial infarction, arterial plaque rupture and thrombosis (Blumberg et al. 2013). Additional in vitro, ex vivo, and cell culture investigations provide mechanistic support for a number of cardio-protective actions specifically for cranberry and its constituents, including anti-inflammatory and antioxidant activity of polyphenols (see Antioxidants Effects of Cranberry) and suggest the potential for high in vivo bioactivity.

Care is warranted in the interpretation of a number of polyphenol study findings as many of these employed a variety of products analyzed by a variety of non-homogenous methodologies and assessed by non-validated assays. Additionally, bioactivity of phenolic compounds is dependent on a number of factors including but not limited to the amount consumed, the molecular structure of compounds, constituent co-factors, absorption, and individual metabolism. While the parent structures of polyphenols are only minimally absorbed, absorption of metabolites formed in gut flora is enhanced. What has not yet been determined is the level and type of the most protective polyphenols in the diet, though a number of studies compare the flavonoids, phenolic, and PAC composition of cranberry to other flavonoid-rich foods (see Phenolic Composition of Cranberry and Del Rio et al. 2013; Khoo and Falk 2014; Wallace 2014, among others). Additionally, a number of studies utilize products that have been fortified with vitamin C or other antioxidants and so require specific consideration when interpreting results.

Flavonoid Consumption Patterns

The total daily intake of flavonoids in the American diet is estimated to be between 189.7 to 209 mg/day (Chun et al. 2007; 2010). The total daily intake of PACs in the American diet is variably estimated at a low mean of 57 mg/d (Gu et al. 2004) to a mean of 95 mg/d (Wang et al. 2011). Relative to dietary surveys of other nations, these values are considered low; for example, the estimated dietary flavonoid intake in