REVIEW ARTICLE

Drugs 2009; 69 (7): 775-807
0012-6667/09/0007-0775/$55.55/0

Cranberry and Urinary Tract Infections

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Contents

Abstract

Urinary tract infection (UTI) refers to the presence of clinical signs and symptoms arising from the genitourinary tract plus the presence of one or more micro-organisms in the urine exceeding a threshold value for significance (ranges from 10^2 to 10^3 colony-forming units/mL). Infections are localized to the bladder (cystitis), renal parenchyma (pyelonephritis) or prostate (acute or chronic bacterial prostatitis). Single UTI episodes are very common, especially in adult women where there is a 50-fold predominance compared with adult men. In addition, recurrent UTIs are also common, occurring in up to one-third of women after first-episode UTIs. Recurrences requiring intervention are usually defined as two or more episodes over 6 months or three or more episodes over 1 year (this definition applies only to young women with acute uncomplicated UTIs).

A cornerstone of prevention of UTI recurrence has been the use of low-dose once-daily or post-coital antimicrobials; however, much interest has surrounded non-antimicrobial-based approaches undergoing investigation

such as use of probiotics, vaccines, oligosaccharide inhibitors of bacterial adherence and colonization, and bacterial interference with immunoreactive extracts of *Escherichia coli*. Local (intravaginal) estrogen therapy has had mixed results to date.

Cranberry products in a variety of formulations have also undergone extensive evaluation over several decades in the management of UTIs. At present, there is no evidence that cranberry can be used to treat UTIs. Hence, the focus has been on its use as a preventative strategy. Cranberry has been effective *in vitro* and *in vivo* in animals for the prevention of UTI. Cranberry appears to work by inhibiting the adhesion of type I and P-fimbriated uropathogens (e.g. uropathogenic *E. coli*) to the uroepithelium, thus impairing colonization and subsequent infection. The isolation of the component(s) of cranberry with this activity has been a daunting task, considering the hundreds of compounds found in the fruit and its juice derivatives. Reasonable evidence suggests that the anthocyanidin/proanthocyanidin moieties are potent antiadhesion compounds. However, problems still exist with standardization of cranberry products, which makes it extremely difficult to compare products or extrapolate results. Unfortunately, most clinical trials have had design deficiencies and none have evaluated specific key cranberry-derived compounds considered likely to be active moieties (e.g. proanthocyanidins). In general, the preventive efficacy of cranberry has been variable and modest at best. Meta-analyses have established that recurrence rates over 1 year are reduced approximately 35% in young to middle-aged women. The efficacy of cranberry in other groups (i.e. elderly, paediatric patients, those with neurogenic bladder, those with chronic indwelling urinary catheters) is questionable. Withdrawal rates have been quite high (up to 55%), suggesting that these products may not be acceptable over long periods. Adverse events include gastrointestinal intolerance, weight gain (due to the excessive calorie load) and drug-cranberry interactions (due to the inhibitory effect of flavonoids on cytochrome P450-mediated drug metabolism). The findings of the Cochrane Collaboration support the potential use of cranberry products in the prophylaxis of recurrent UTIs in young and middle-aged women. However, in light of the heterogeneity of clinical study designs and the lack of consensus regarding the dosage regimen and formulation to use, cranberry products cannot be recommended for the prophylaxis of recurrent UTIs at this time.

Urinary tract infection (UTI) refers to the presence of clinical signs and symptoms arising from the genitourinary tract plus the presence of one or more micro-organisms in counts exceeding a threshold value (usually 10^2–10^3 colony forming units [cfu]/mL). Infections are usually localized to the bladder (cystitis), kidneys (pyelonephritis) or prostate (acute or chronic bacterial prostatitis). UTIs are common, with adult women having about a 50-fold increase in risk compared with adult males. Recurrent UTIs are classified as either relapses (wherein the same organism[s] as in the previous UTI lead to recurrence) or re-infections (wherein [a] new organism[s] lead to recurrence). Recurrent UTIs (defined as two or more episodes over 6 months or three or more episodes over 1 year) occur in up to one-third of women after first-episode UTIs. This definition of recurrent UTIs applies only to young women with acute uncomplicated UTIs.

The vast majority of UTIs arise from organisms colonizing the lower genitourinary tract. The initial step involves colonization of the periurethral area with uropathogen(s) followed by ascension of these organisms up the urethra. Infection arises from bacterial growth within the usually sterile urinary tract. The second step involves adherence of bacteria to the uroepithelial mucosa.[1]

A cornerstone of prevention of UTI recurrence has been the use of low-dose once-daily or post-coital antimicrobials such as cotrimoxazole (trimethoprim/sulfamethoxazole), trimethoprim, nitrofurantoin or a fluoroquinolone. However, several non-antimicrobial-based approaches to the prevention of UTIs are undergoing investigation, including lactobacilli and other probiotics; vaccines; oligosaccharide inhibitors of bacterial adherence, colonization and infection; bacterial interference using immunoreactive extracts of *Escherichia coli*; and intravaginal estrogen therapy.[1-3]

Cranberries, the focus of this article, have been extensively evaluated for their therapeutic effect in a wide variety of maladies in humans. Areas in which therapeutic potential exists include cardioprotection,[4,5] protection against cancer (active against breast, colon, prostate, lung, cervical, melanoma, pancreatic, oral and leukaemic cell lines),[5] protection against tooth decay,[6-13] protection against gastrointestinal disorders associated with *Helicobacter pylori* infection[10] and antiviral activity (vs reovirus, rotavirus and influenza virus).[14-16]

However, cranberries (particularly in the form of cranberry juice) have been evaluated and used most widely over several decades in the prevention and treatment of UTIs. Despite decades of investigation, there is little consensus regarding most facets of cranberries as guardians of urogenital health. The purpose of this article is to review all relevant English language studies of cranberries in the areas of chemistry, mechanism of action, pharmacodynamics, pharmacokinetics, clinical efficacy/tolerability, drug-cranberry interactions and dosage regimens. Pertinent papers were located by searching MEDLINE via PubMed and EMBASE from 1950 to December 2008. Further articles were located through a review of the bibliographies of retrieved articles.

Although blueberry juice inhibits the adhesion of *E. coli* strains with type I and P-fimbriae to uroepithelial cells in a manner similar to that seen with cranberry juice (see section 4),[17] there are no clinical data with this product and so it is not discussed further.

1. Botany

Cranberry is a plant from the family Ericaceae and is known as *Vaccinium macrocarpon*, *V. oxycocus* and *V. eruthrocarpum*. Cranberry is derived from a contraction of 'crane berry'; this name comes from its bilberry flower, which, when it withers, is similar in appearance to the head and neck of the sand crane, a bird which often feeds on the berries of this plant. The flower is white or light rose in colour and bell shaped. The small, red berries form in June or July in the Northern Hemisphere. The fruit is pulpy, with the pericarp being soft, parenchymatous and sour.[18,19]

This small evergreen shrub originated in the north-eastern US near Cape Cod and grows in acid swamps (bogs) full of peat moss in humid forests. It is rarely grown in home gardens. It has been used by native peoples for thousands of years as a flavouring aid (for dried meat) and as a medicine. It has also been used by sailors to prevent scurvy owing to its high vitamin C content.[18,19]

Ninety percent of the world's annual production (50 million tons = 200 billion fruits) comes from the states of Massachusetts, New Jersey and Wisconsin in the US, and 8% comes from the provinces of Quebec and British Columbia in Canada. The fruit is harvested in September and October. In 1997, cranberry was in the 'top ten' of remedies sold by herbalists in the US. The usual preparations include fresh whole berries, gelatinized products, juices (these are usually 10–25% v/v pure juice) and capsules. Pure juice is too acidic (pH ≤2.5) and unpalatable, even when diluted with traditional sweetening vehicles.[18,19]

Table I. Chemical constituents of cranberry[21,22,24,26]

Organic acids	Flavonoids	Iridoid glycosides	Anthocyanidins
Benzoic acid	(–)-epicatechin	Monotropein	Peonidin[h]
O-hydroxybenzoic acid	Catechin	6,7-dihydromonotropein	Cyanidin[h]
M-hydroxybenzoic acid	Quercetin[a]	Coumaroyl	Pelargoniding[i]
P-hydroxybenzoic acid	Methoxyquercetin[b]		Petuniding[i]
2,3-dihydroxybenzoic acid	Myricetin[c]		Proanthocyanidins (trimer A-type, dimer A-type, dimer B-type)
Trans-cinnamic acid	Methoxymyricetin[d]		
O-hydroxycinnamic acid	Dimethoxymyricetin[e]		
3-O-P-hydroxycinnamoyl ursolic acid	Prunin[f]		
O-phthalic acid	Phloridzin[g]		
Vanillic acid			
P-coumaric acid			
Ferulic acid			
Caffeic acid			
Sinapic acid			
Trans-resveratrol			
Quinic acid			
Malic acid			
Shikimic acid			
Citric acid			

a Including the 3-β-galactoside, 3-β-glucoside, 3-α-xylopyranoside, 3-α-arabinopyranoside, 3-α-arabinofuranoside, 3-rhamnopyranoside, 3-O-(6′′-p-coumaroyl)-β-galactoside and 3-O-(6′′-benzoyl)-β-galactoside forms.

b Including the pentoside, 3-α-xylopyranoside and 3-β-galactoside forms.

c Including the 3-β-galactoside, 3-α-xylopyranoside and 3-α-arabinofuranoside forms.

d Pentoside form.

e Hexoside form.

f Naringenin 7-glucoside.

g Phloretin 2′-O-glucose.

h Including the 3-O-arabinoside, 3-O-galactoside and 3-O-glucoside forms.

i Minor component.

2. Composition of Cranberry

Cranberries are composed of 88% water and a complex mixture of organic acids, vitamin C, flavonoids, anthocyanidins, catechins and triterpinoids.[2,18,19] In fact, the biologically active subfraction of the low-polarity concentrate fraction has at least 248 individual constituents.[20]

At least 14 organic acids are represented in cranberries (table I).[21,22] Salicylic acid is also found in cranberry juice, in a concentration of approximately 7 mg/L.[23] The hydrophilic fraction of cranberry juice contains quinic, malic, shikimic and citric acids in concentrations of 2.67–3.57% w/v.[21] At least 22 distinct types of flavonoids are found in cranberry powder (table I), with quercetin and myricetin being the most prevalent (table I).[24,25] The iridoid glycosides are responsible for the taste of cranberry products.[21] Vitamin C is found at high levels in cranberries (200 mg/kg fresh berries).[25]

The anthocyanidins and proanthocyanidins are tannins (stable polyphenols) found only in vaccinium berries (cranberries, blueberries). These function as a natural plant defence system against microbes. The cyanidin content varies between cranberries and blueberries, with cranberries containing primarily epicatechins.[2,18,19]

In cranberry juice, the 3-O-arabinoside (35.3%) and 3-O-galactoside (26.8%) forms of peonidin, and 3-O-arabinoside (16.1%) and 3-O-galactoside (19.7%) forms of cyanidin are the major anthocyanidins.[26] The proanthocyanidins are thought to be the main active constituents in cranberry, acting to prevent the adherence of uropathogenic type I and P-fimbriated *E. coli* to the urogenital mucosa (see section 4). They are a series of polyflavan-3-ol oligomers with primarily epicatechin units, predominantly in the form of tetramers (49%) and pentamers (37%). They exist in 2,3-cis stereochemical form containing at least one A-type (C4/C8) interflavonyl linkage. The most common terminating unit is procyanidin A2 (this is 4-fold more common than a termination with an epicatechin monomer). Their mean molecular weight is approximately 1354 Da. Again, although they can be 4–10 epicatechin units in length, most are four or five such units in length.[27,28]

3. Pharmacodynamics of Cranberry

3.1 Antimicrobial Activity

Table II illustrates the *in vitro* antimicrobial activity of cranberry against a wide variety of micro-organisms.[29-36] It is evident that cranberries, in the main, have no useful antimicrobial activity. In addition, the only single constituent of cranberry juice tested, 1-O-methylgalactose, was found not to have antibacterial activity.[20]

3.2 Inhibition of Adherence to Surfaces

The effect of cranberry juice cocktail (25% pure juice) on the adherence of 14 *E. coli* strains to three cell lines (Y1 mouse adrenal cortex tumour cells, resident mouse peritoneal macrophages and Chinese hamster ovary cells) was investigated. Thirteen of these strains had type I fimbriae and five had P-fimbriae. A 1 : 2 dilution of the cocktail almost completely inhibited type I fimbriae-mediated adherence of eight *E. coli* strains. Dilutions of 1 : 12 to 1 : 50 produced approximately 50% inhibition. Inhibition of type I fimbriae-mediated adherence was uniform between cranberry product lots. It was also linear in all three cell lines over a range of log dilutions of 0.25–2. Inhibition of type I fimbriae-mediated adherence was also similar for the three cell lines (data not shown). A 1 : 2 dilution of the cocktail also inhibited P-fimbriae-mediated adherence but this inhibition varied between cranberry product lots. In summary, cranberry juice cocktail contained two types of type I fimbriae inhibitors, one dialyzable (thought to be fructose) and one non-dialyzable plus one type of P-fimbriae inhibitor (non-dialyzable).[37]

Freshly prepared juice, cranberry juice cocktail and cranberry concentrate were compared with respect to their abilities to inhibit adherence of one clinical *E. coli* isolate to human uroepithelial and buccal cells. Undiluted and 1 : 2, 1 : 3, 1 : 5, 1 : 10, 1 : 100 and 1 : 1000 dilutions of all three cranberry products were analysed. All except the 1 : 1000 dilutions significantly reduced *E. coli* adherence to both cell lines. Inhibition was dose-related (>97% with undiluted → 30% with 1 : 100 dilutions; $p < 0.05$). In a second experiment, of 134 clinical *E. coli* isolates, 77 adhered to uroepithelial cells and 71 adhered to buccal cells. Cranberry juice exposure produced ≥75% inhibition of adherence in 50 of 77 (65%) uroepithelial and 43 of 71 (61%) buccal cells.[30]

Adherence/antiadherence activities of cranberry juice were examined in 145 bacterial isolates (63 *E. coli* [31 non-urinary, 32 urinary], 32 *Proteus* spp. [23 non-urinary, 9 urinary], 15 *Klebsiella* spp. [14 non-urinary, 1 urinary], 5 *Enterobacter* spp. (all non-urinary) and 30 *Pseudomonas aeruginosa* strains [19 non-urinary, 11 urinary]). For *E. coli*, *Proteus* spp. and *P. aeruginosa*, urinary isolates adhered more than did non-urinary isolates to uroepithelial cells but statistical significance was seen only with *E. coli* (this difference was 3-fold in magnitude). When eight bacterial isolates were pre-incubated with the juice cocktail, adherence significantly fell in seven of eight isolates (2/2 adherent urinary *E. coli*, 1/2 adherent urinary *Proteus* spp., 2/2 adherent urinary *P. aeruginosa* and 2/2 non-urinary *E. coli* [all $p < 0.05$]). Pre-incubation of uroepithelial cells with the juice cocktail produced significant reductions in adherence for only three isolates (1 *E. coli*, 1 *Proteus* spp. and 1 *P. aeruginosa*). The magnitude of effect was also

Table II. *In vitro* antimicrobial activity of cranberry

Study (year)	Preparations and test conditions	Micro-organisms	Results
Gupta et al.[29] (2007)	Juice concentrate in synthetic urine (0%, 12.5%, 25%)	UPEC (2 *pap*C-positive, 1 *pap*C-negative strains)	12.5% and 25% dilutions produced statistically similar growth inhibition against all 3 strains. No significant relationship between effect of juice concentrate on bacterial growth and effect on biofilm formation on inert surfaces
Sobota[30] (1984)	Freshly prepared juice in culture medium (33%)	*Escherichia coli* (134 unselected clinical isolates)	No effect on growth
Ahuja et al.[31] (1998)	Juice concentrate in culture medium (25%)	*E. coli* JR1 *E. coli* DS17 (P-fimbriated strains)	No effect on growth
Valentova et al.[32] (2007)	Dried cranberry juice powder (200 mg = 5 g fresh cranberries) used in standard microdilution plate MIC methodology	Variety of hospital isolates (*Staphylococcus aureus*, MRSA, VR *Enterococcus faecium*, *Klebsiella pneumoniae*, etc.)	Virtually nil activity (MICs 179–357 mg/mL) [*P. aeruginosa* most susceptible]
Lee et al.[33] (2000)	5-Fold-concentrated preparation of juice (to simulate concentrate) in culture medium (50%)	7 ATCC strains: *E. coli* ATCC 29522 *S. aureus* ATCC 29213 *Pseudomonas aeruginosa* ATCC 27853 *Enterococcus faecalis* ATCC 29212 *K. pneumoniae* ATCC 13883 *Proteus mirabilis* ATCC 7002 *Salmonella enteritidis* ATCC 14028	5/7 strains had no growth at 24 h while *E. faecalis* and *S. enteritidis* had reduced counts compared with unsupplemented media. Some activity noted in dilutions as high as 1 : 32
Allison et al.[34] (2000)	Cranberry extract (prepared from fresh cranberries) resuspended in 0.1 mol/L ammonium bicarbonate buffer	"Wide range of Gram-negative and Gram-positive bacteria (data not shown)''	No effect on growth
Cavanagh et al.[35] (2003)	Juice diluted 1 : 5 with culture media (16.7%)	12 strains (University of New South Wales, Australia collection):	Degrees of growth inhibition:
		Alcaligenes faecalis	100%
		Clostridium perfringens	25%
		E. faecalis	100%
		E. coli	92%
		Mycobacterium phlei	100%
		P. aeruginosa	75%
		Salmonella california	25%
		S. enteritidis	25%
		Salmonella typhi	75%
		Shigella sonnei	100%
		S. aureus	84%
		MRSA	100%
	Juice diluted 1 : 10 with culture media (9.1%)	*E. coli*	50% Only these 5 strains were inhibited by the noted degrees of growth inhibition
		M. phlei	100%
		S. typhi	12%
		S. aureus	25%
		MRSA	12%

Continued next page

Table II. Contd

Study (year)	Preparations and test conditions	Micro-organisms	Results
	Juice diluted 1 : 100 with culture media (0.99%)		No effect on any strain
Leitao et al.[36] (2005)	Anthocyanidin- and proanthocyanidin-rich fractions from juice concentrate	*E. coli* *Micrococcus luteus* *P. aeruginosa* *S. aureus* ATCC 25923 *E. faecalis* *Streptococcus mutans* *S. mutans* 1.1 *S. mutans* 3.1	No activity of any fraction against these 8 micro-organisms
		S. aureus ATCC 6538	4/10 fractions had some activity (6 mm zone of inhibition with 50 mg/L of fractions 1, 6, 7; 8 mm zone with 50 mg/L of fraction 10). Whole fractions A + B were inactive against all 9. Whole fraction C produced a 7 mm zone with the 2 *S. aureus* strains and a 6 mm zone with the 1 enterococcal strain. 96% pure juice (adjusted to pH 7.0) was inactive against all 9. 96% pure juice (unadjusted pH) had some antibacterial activity (17 mm zone with *M. luteus*, 8 mm zone with *S. aureus* ATCC 6538, 7.5 mm zone with *S. aureus* ATCC 25923)

MIC = minimum inhibitory concentration; **MRSA** = meticillin-resistant *S. aureus*; **UPEC** = uropathogenic *E. coli*; **VR** = vancomycin-resistant.

significantly reduced compared with that seen with pre-incubation of bacteria with the juice cocktail. Juice cocktail also reduced the adherence of pre-attached bacteria (adherent *E. coli* strain), even during the first minute after adding the juice cocktail ($p < 0.01$). The maximal detachment possible was approximately 70% of the pre-attached load.[38]

Two studies have evaluated the effect of cranberry on the adhesion of *E. coli*, *Staphylococcus aureus*, *Salmonella typhimurium*, *Campylobacter jejuni* and *Listeria monocytogenes* to glass (borosilicate) cover slips. This model is felt to be a reasonable surrogate for foreign (device) surfaces in the urinary tract. Cranberry juice reduced the nonspecific adhesion of *E. coli*, *S. aureus* and *S. typhimurium* but not *C. jejuni* or *L. monocytogenes*. White cranberry juice had no effect; only red juice. A slightly hydrophobic molecule of molecular weight >5000 was the active moiety.[39] In the second study, the effect of a cranberry extract (prepared from fresh cranberries) resuspended in 0.1 mol/L ammonium bicarbonate buffer and adjusted to pH 7.0 on the adherence of *E. coli* ATCC 8739 to glass coverslips was evaluated. Incubation of *E. coli* for 2 hours in the presence of the cranberry extract reduced the strength of adherence but only at the highest concentration tested (1 : 10 dilution), not at a 1 : 100 dilution.[34]

In a model more directly related to urinary tract biomaterials, the effect of high-molecular-weight proanthocyanidins (PACs) on the adhesion of uropathogenic *E. coli* and *Enterococcus faecalis* to polyvinyl chloride (PVC) and polytetrafluoroethylene (PTFE) was evaluated. A parallel-plate flow chamber was the model utilized. Bacterial attachment to both surfaces was significantly reduced when either the bacteria or the surfaces or both were pretreated with PACs (greatest degree of inhibition occurred when both were pretreated). For example, the fold reductions in bacterial adherence of *E. coli* to PVC when bacteria, biomaterial and both were pretreated with PACs were 1.5, 1.6 and 1.8, respectively. Corresponding values for *E. coli* adherence to PTFE were 1.8, 1.7 and 2.1. Of interest, *E. faecalis* adherence was also reduced in this

model. The fold reductions in bacterial adherence of *E. faecalis* to PVC when bacteria and biomaterial were pretreated with PACs were 1.4 and 2.0, respectively. When PTFE was pretreated with PACs, *E. faecalis* adherence fell 56%. When PVC and bacteria, and PTFE and bacteria were pretreated with PACs, *E. faecalis* adherence fell 90% and 88%, respectively. This effect was non-biospecific, since inhibition also occurred when latex microspheres were substituted for bacteria. The PVC surface was readily coated with PACs (coverage was 600 ng/cm^2 with a film thickness of approximately 5 nm). The effect of PACs was not electrostatically mediated. Nor could the bacteria-surface interaction be explained by the Derjaguin-Landau-Verwey-Overbeek (DLVO) model. The steric stabilization model explained the observed experimental data much better than the DLVO model.[40]

Of interest, the adherence of the oral pathogens *Streptococcus mutans* and *Porphyromonas gingivalis* to hydroxyapatite and surfaces coated with type I collagen, fibrinogen and human serum, respectively, was significantly inhibited by cranberry.[12,41]

In summary, cranberry inhibits the adhesion of a variety of pathogens to a variety of surfaces in a dose-dependent fashion. Most studies evaluated uropathogenic type I and/or P-fimbriated *E. coli*. However, adherence of urinary isolates of *Proteus* spp. and *P. aeruginosa*, as well as *S. aureus*, *S. typhimurium* and *E. faecalis* isolates to surfaces could also be inhibited by cranberry (latter three only tested with glass, PVC and/or PTFE). Human uroepithelial cells provided the surfaces of interest in most studies. However, bacterial attachment to murine adrenal cortex tumour cells, resident murine peritoneal macrophages, Chinese hamster ovary cells, human buccal cells, hydroxyapatite, surfaces coated with type I collagen/fibrinogen/human serum and foreign device models of borosilicate glass, PVC and PTFE could also be inhibited by cranberry. Cranberry could prevent bacterial adherence to cells as well as cause detachment of adherent bacteria from cells.

Experiments have been performed to identify the component(s) of cranberry responsible for its antiadherence activity with uroepithelial and other cell types. Experiments to identify active metabolites and/or individual constituents are important, as *in vitro* testing with whole cranberry products probably has little relevance to *in vivo* activity. This is because the constituents in the whole cranberry products may not be the same as those entering the urine. For example, intact proanthocyanidins may not be active *in vivo*, since they are too large to be absorbed as intact molecules in the gastrointestinal tract and hydrolysis at gastrointestinal tract pH to absorbable moieties is unlikely to occur. Even if hydrolysis were to occur, first-pass extraction by the liver might be expected to substantially alter these products of hydrolysis. Phenolic metabolites probably exist at too low a concentration *in vivo* to be active or, at least, to be as active as other moieties.[42]

In one experiment, a commercially available cranberry powder (standardized to 9 mg proanthocyanidins per gram of powder) and a proanthocyanidin extract from cranberries were compared. Adherence studies utilized *E. coli* IA2 (a wild-type, class 2, P-fimbriated UPEC strain) as well as bladder and vaginal epithelial cells. Inhibition of adherence to bladder mucosa occurred in a linear, dose-dependent fashion over a proanthocyanidin concentration range of 5–75 mg/L ($p < 0.001$). Pre-incubation of vaginal epithelial cells with cranberry powder significantly reduced mean adherence from 18.6 to 1.8 bacteria per cell ($p < 0.001$).[29] Another trial found the proanthocyanidins to have potent antiadherence activity *in vitro*, at concentrations down to 75 mg/L.[27] Antiadherence with dried cranberry juice (NutriCran-90®: 200 mg dried cranberry juice/solid dose administration unit = 5 g fresh cranberries) had a threshold concentration range of 0.037–0.12 mg/mL, with markedly reduced adherence when concentrations exceeded 2.4 mg/mL.[32] The active subfraction of the low-polarity concentrate fraction of cranberry juice dose-dependently inhibited adherence at concentrations of 200 and 400 μg/mL but not at 100 μg/mL.[20] Using a cranberry proanthocyanidin extract (pH 6.5), 2-fold dilutions were tested to establish the effects on the adhesion

of 39 P-fimbriated UPEC isolates to uroepithelial cells. Adhesion of all 39 isolates was inhibited at concentrations ranging from 6 to 375 mg/L.[43] Lastly, A-linked (cranberry) and B-linked (grape, apple, tea, chocolate) proanthocyanidins were compared for antiadherence activities *in vitro* against P-fimbriated UPEC isolates. A-linked proanthocyanidins were antiadherent at concentrations of ≥60 μg/mL. B-linked proanthocyanidins from grapes exhibited minor antiadherent activity at a concentration of 1200 μg/mL, while all other B-linked compounds were inactive.[28]

In another experiment, A-linked proanthocyanidins were isolated from ripe cranberries and monomers, dimers and trimers were compared in terms of their antiadherence effects on P-fimbriated UPEC. Monomers and dimers were only weakly active or were inactive. Only trimers were active at low concentrations: epicatechin-(4β→6)-epicatechin-(4β→8,2β→0→7)-epicatechin and epicatechin-(4β→8,2β→0→7)-epicatechin-(4β→8)-epicatechin at 0.6, 1.2 and 2.4 ng/mL and epicatechin-(4β→8)-epicatechin(4β→8,2β→0→7)-epicatechin at 1.2 and 2.4 ng/mL.[44] Fructose, vitamin C and 1-O-methylgalactose, all constituents of cranberry juice, had minimal to no effect on *in vitro* adherence to mucosal surfaces.[20,30]

AS/K1 mice were randomized to receipt of a standard diet (n = 15) or a diet in which cranberry juice cocktail replaced water (n = 15). Treatment proceeded for 14 days and urine was collected on multiple days. Adherence of *E. coli* to uroepithelial cells was significantly reduced in the cranberry juice cocktail-ingesting mice compared with the control mice on all six study days (all $p < 0.01$).[30]

In summary, the only active moieties of cranberry discovered to date are the trimeric A-type proanthocyanidins, which can be isolated and tested in their pure forms *in vitro* and *in vivo*.

3.3 Inhibition of Biofilm Formation

Cranberry inhibits biofilm formation by the oral pathogens *S. mutans* and *P. gingivalis*.[12,41] In addition, juice concentrate (in concentrations of 0 as control, 12.5% and 25% in synthetic urine) dose-dependently inhibited biofilm formation by two *papC*-positive strains of UPEC, while in the one *papC*-negative strain of UPEC, only the 25% concentration inhibited formation. No significant relationship was noted between the juice concentrate effect on bacterial growth and the effect on biofilm formation on inert surfaces.[45]

An open-label, crossover trial was conducted in 15 patients with spinal cord injury and neurogenic bladder. Patients received 250 mL of water three times daily with meals for 7 days, followed by a 1-day washout period, then cranberry juice cocktail 250 mL three times daily with meals for 7 days. Biofilm load for each patient was calculated as the percentage of 50 uroepithelial cells with biofilm present. On days 0, 7 and 15, mean ± SD biofilm loads (i.e. percentage of cells with biofilm present) were 20.26 ± 25.5, 10.06 ± 28.9 and 5.62 ± 7.03, respectively. Cranberry supplementation produced a significant reduction in biofilm load compared with baseline ($p = 0.013$) and compared with the water phase ($p = 0.028$).[46]

Another open-label, crossover trial was conducted in two healthy males who received single 1 L doses of cranberry juice (SDV®, Cognac, France) and mineral water, with a 3-day washout period between phases. First-morning urine samples were collected to measure biofilm formation on inert surfaces by three UPEC strains (all three had type I pili and two of three were *papC*-positive). In subject A, cranberry juice produced a significant reduction in biofilm formation but only with the two *papC*-positive strains. In subject B, cranberry juice produced a significant reduction in biofilm formation but only with the one *papC*-negative strain. The effect on biofilm formation was not significantly correlated with the fall in urine pH seen with juice ingestion (from pH 7.0 to pH 5.0).[45]

An *in vitro* model of the catheterized bladder was used to investigate the effect of cranberry juice on crystalline catheter-blocking *Proteus mirabilis* biofilms. A group of 24 healthy volunteers were randomized to drink one or two 500 mL volumes of either water or cranberry juice, and urine was collected for the subsequent 8 hours. These urine samples together with artificial urine were then tested with *P. mirabilis* NSMG, a clinical isolate from an encrusted catheter, in the *in vitro* model. Calcium and

magnesium encrustation amounts on the catheters were not significantly different under the two experimental conditions when 500 mL volumes were ingested. When 1000 mL was ingested, encrustation was significantly less in the water compared with cranberry juice condition ($p = 0.007$). In both conditions of water and cranberry supplementation, the encrustation amounts were significantly lower than that on catheters in models supplied with urine from non-fluid-supplemented volunteers ($p < 0.001$). Using simulated fluid intakes of 720, 2160 and 4320 mL/24 hours, encrustations were significantly reduced at the two higher simulated intakes compared with the 720 mL/24 hours intake ($p < 0.01$). At simulated fluid intakes of 720 and 4320 mL/24 hours, catheters in the former condition became blocked with encrustations after a mean of 42.5 hours, whereas in the latter condition, catheters drained freely for more than 10 days. This study demonstrated that cranberry juice did not produce urine inhibitory to the development of crystalline *P. mirabilis* biofilms. The important factor in preventing catheter encrustation was a high fluid intake.[47]

In summary, preliminary data suggest that cranberry exposure inhibits biofilm production but does so selectively. Biofilms produced by oral pathogens and uropathogenic *E. coli* appear to be susceptible to inhibition, whereas those produced by catheter-blocking *P. mirabilis* are not.

3.4 Effects on Urine Composition

A number of studies have examined the effect of cranberry on urine composition, to define its mechanism of action in the prevention of UTIs and its potential to produce nephrolithiasis as an adverse drug event (ADR) [for more on latter, see section 7].

Neither single doses (ranging from 1200 to 4000 mL of cranberry juice cocktail and 100–305 g of fresh cranberries) nor multiple-dose regimens (1200 mg/day of cranberry solids [Cranactin®] for 2.5 days, 22–54 g/day of fresh cranberries for up to 3 days and 1200–4000 mL/day of cranberry juice cocktail for up to 6 days) had a clinically significant effect on urine pH.[48-56] Titratable acidity was increased by single doses of 1200 mL (30%), 1500 mL (9%) and 4000 mL (77%) of cranberry juice cocktail and 100 g (9%), 150 g (5%), 200 g (–7%), 250 g (2%) and 300–305 g (18%) of fresh cranberries.[49-51] Corresponding increases in organic acids were 22%, 29% and 26% for cranberry juice cocktail, and 23%, 32%, 35%, 35% and 48% for fresh cranberries.[49-51] For multiple-dose regimens, titratable acidity was increased by 2–4 days of 1500 mL/day (25%), 2000 mL/day (15%), 2500 mL/day (37%) and 4000 mL/day (–7%) of cranberry juice cocktail.[52] Hippuric acid daily excretion was increased by 508% after ingestion of 305 g of fresh cranberries.[51] Blood alkali reserve fell by 20%, 45% and 63% after single 100, 200 and 300 g doses of fresh cranberries.[50] Cranberry juice capsules (Cranactin®) 400 mg three times daily for 2.5 days increased mean urine surface tension by 11.5% (as compared with the mean 8.0% increase with water supplementation).[56]

3.5 Miscellaneous Effects

An *in vivo* nematode killing model was used to test the virulence of four uropathogenic *E. coli* strains (NECS20575 and NECS29787, strains with P-fimbriae and type I pili; NEC5, a CTX-M-15-producing strain without fimbriae or pili; and NEC13, a TEM-3-producing strain with type I pili but no P-fimbriae). The nematode was the Fer15 mutant of *Caenorhabditis elegans*. After inoculation with *E. coli*, these worms were grown in urine samples collected after placebo or cranberry (108 mg single dose) ingestion by eight healthy female volunteers (see table III for details). The mean time for 50% of the worms to be killed was increased significantly for worms inoculated with the two NECS and the NEC13 strains when grown in urine samples collected after cranberry administration as compared with placebo administration (5.43 vs 3.21, 5.11 vs 3.03 and 5.28 vs 4.76 days, respectively; $p < 0.001$, $p < 0.001$ and $p = 0.02$). This was also reflected in the significant prolongation in the times for all worms to die, again for worms inoculated with the same three *E. coli* strains, grown in urine samples collected after cranberry versus placebo ingestion. Thus, results of this study suggest that cranberry exposure was able to reduce the

Table III. Pharmacodynamics of cranberry administration in humans[a]

Study (year) and design	Population (no.)	Treatment	Results
Bodel et al.[49] (1959) ol	Healthy volunteers (no number reported)	Single 1200–4000 mL doses of cranberry juice cocktail	Freshly voided urine had no activity against growth of *Escherichia coli* at the pH at which it was voided. When urine was adjusted to pH 5.0, only specimens with a hippuric acid concentration >0.020 mol/L were bacteriostatic against the 1 freshly isolated *E. coli* strain (no other details available regarding the organism)
Di Martino et al.[45] (2005) ol, co	Healthy male volunteers (2)	Single 1 L doses of cranberry juice (SDV®, Cognac, France) and mineral water, 3 days apart	First morning urine was collected to evaluate effect of urine on growth of 3 UPEC strains (all with type I pili and two-thirds were *papC*-positive). Growth significantly ↓ after juice only with 1 strain in each subject. No significant correlation between (1) juice effects on biofilm formation and growth and (2) pH reduction after juice intake (from 7.0 to 5.0) and effect on growth
Tong et al.[59] (2006) ol	Healthy Chinese volunteers (5 male, 5 female)	750 mL water on day 1 → 750 mL cranberry juice concentrate on day 2	Using *E. coli* ATCC 25922 as the test organism, urine after placebo and juice were NS different in supporting bacterial growth (lag phases were ~2 h and growth rate constants were NS different)
Sobota[30] (1984) ol	Healthy volunteers (9 male, 13 female)	15 oz cranberry juice cocktail × 1	In urine samples 1–3 h post-ingestion, adherence of *E. coli* to uroepithelial cells was significantly reduced in 15/22 (68%). Hippuric acid concentration achieved was a maximum of 0.02 mol/L (this compound produced no inhibition of adhesion *in vitro* over a concentration range of 0.001–0.05 mol/L)
Schmidt and Sobota[38] (1988) ol	Healthy volunteer (1)	12 oz cranberry juice cocktail (OceanSpray®) ingested → urine collected 2 h after	Tested 2 adherent *E. coli*, 2 adherent *Proteus* spp., 2 adherent *Pseudomonas aeruginosa* and 2 non-urinary *E. coli* (n = 8). When urine was pre-incubated with bacteria, all isolates demonstrated a significant ↓ in adherence to uroepithelial cells (all $p < 0.05$). When urine was pre-incubated with uroepithelial cells collected 2 h post-juice, a significant ↓ in adherence was seen in 6/8 (75%) isolates (1 each of *E. coli* and *Proteus* spp. did not respond)
Habash et al.[56] (1999) ol, co	Healthy male volunteers aged 25–40 y (10)	All received: 1. water 500 mL tid × 2 days → 500 mL on day 3 (in morning) 2. vitamin C 500 mg bid × 2 days → 500 mg on day 3 (in morning) 3. cranberry juice capsules (Crenactin®) 400 mg tid × 2 days → 400 mg on day 3 (in morning) A 4.5-day washout period occurred between study phases. Entire study was repeated 2 more times	Test organisms all bound to silicone rubber (*E. coli* Hu 734, *Enterococcus faecalis* 1131, *Staphylococcus epidermidis* 3081, *P. aeruginosa* AK1 and *Candida albicans* Urine 1 [a unique strain]). There was a significant ↓ in the mean initial deposition rate of *E. coli* after cranberry vs water ingestion. At 4 h, the same trend was occurring but was NS. The mean initial deposition rates for all organisms except *P. aeruginosa* were ↓ with cranberry vs vitamin C and for all organisms except *P. aeruginosa* and *C. albicans* with cranberry vs water (no statistical analysis provided). The number of adherent organisms after 4 h was ↓ with cranberry vs vitamin C (for *E. coli* and *C. albicans* but not *E. faecalis*) and for cranberry vs water (for all 3 organisms) [no statistical analysis provided]. One question was whether water diluted Tamm-Horsfall protein, leading to ↑ adhesion

Continued next page

Table III. Contd

Study (year) and design	Population (no.)	Treatment	Results
Reid et al.[46] (2001) ol, co	SCI patients (15)	Water 250 mL tid with meals × 7 days → nothing × 1 day → cranberry juice 250 mL tid with meals × 7 days	Adhesion of Gram-negative bacteria to uroepithelial cells fell significantly after juice compared with water ($p = 0.033$) but fall in Gram-positive bacterial adhesion was NS. Adhesion of Gram-positive bacteria to uroepithelial cells fell significantly after juice compared with baseline ($p = 0.022$) but fall in Gram-negative bacterial adhesion was NS
Howell and Foxman[43] (2002) ol	Women with UTIs due to P-fimbriated UPEC[b] (39)	Single 240 mL dose of cranberry juice cocktail	Evaluated 12-h pre-juice and 12-h post-juice urine collections for adherence of UPEC to uroepithelial cells. Juice prevented adhesion of 31/39 (80%) UPEC strains and 19/24 (79%) antimicrobial-resistant UPEC strains to uroepithelial cells. Pre-juice urine had no uniform effect on adhesion. Antiadhesion effect was evident within 2 h of juice ingestion and persisted for up to 10 h
Greenberg et al.[60] (2005) ol	Women with culture-confirmed UTI with UPEC (5)	Participants provided 4 urine samples: 1. baseline 2. 2–5 h after 1 box (42.5 g) SunMaid® raisins 3. 5–7 days after #2 4. 2–5 h after 42.5 g sweetened dried cranberries (Craisins®, OceanSpray®)	1/5 UPEC strains from the patients had P-fimbriae. None of the baseline or early and late post-raisin urines had any antiadhesion activity against any of the 5 strains. Post-cranberry urine had an effect on only 1 UPEC strain (↓adhesion of the P-fimbriated strain by 25%). 5 known adherent UPEC strains were also tested. Again, baseline and early and late post-raisin urines had no antiadhesion activity against any of the UPEC strains. Post-cranberry urine produced no effect on 2 strains, 25% ↓ in adherence in 2 strains and 50% ↓ in adherence in 1 strain. Reason for the lack of activity of raisins compared with cranberries was not the fructose content difference (raisins are 33%, cranberries are 25% fructose). It was the 5- to 10-fold difference in proanthocyanidin content in favour of cranberry
Howell et al.[28] (2005) ol, co	Healthy volunteers (2 male, 4 female)	Single doses of: 1. 240 mL cranberry juice cocktail 2. 240 mL purple grape juice 3. 240 mL apple juice 4. 240 mL aqueous extract from 2 g brewed tea (1 bag) 5. 40 g (5 pieces) of dark chocolate 3-day washout periods between phases	Antiadhesive activity vs P-fimbriated *E. coli* was only seen with cranberry juice. Antiadhesive activity ↑ in linear fashion for 0–2, 2–4 and 4–6 h post-dose urine collections (25%, 50%, 75% inhibition). Effect persisted for at least 8 h (50% inhibition during 6–8 h interval). No urine was collected after 8 h (study design flaw). All urine was neutralized to pH 6.5 so acidic pH was not the mechanism
Di Martino et al.[61] (2006) r, db, co	Healthy male and female volunteers (20)	Single doses of: 1. cranberry juice cocktail (OceanSpray®) 750 mL 2. cranberry juice cocktail (OceanSpray®) 250 mL + mineral water 500 mL 3. mineral water 500 mL 4. placebo Washout periods of ≥6 days between phases	First morning urine was collected to evaluate effect of urine on adherence of 6 UPEC strains (all with type I pili, 3 *papC*-negative, 3 *papC*-positive). Juice produced a dose-dependent reduction in adherence to uroepithelial cells. Effect was independent of encoding for type I pili and antimicrobial resistance determinants. Mean ↓ in adherence (250 mL) = 45%, (750 mL) = 62%

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Table III. Contd

Study (year) and design	Population (no.)	Treatment	Results
Valentova et al.[32] (2007) ol, r	Healthy female volunteers aged 19–28 y (65)	Randomized to receive: 1. 400 mg dried cranberry juice (NutriCran-90®) once daily (n = 20) 2. 1200 mg dried cranberry juice/day (400 mg tid) [n = 22] 3. placebo (n = 23) 8 wk study duration	Biofilm with an abundant *E. coli* population was only seen in urines of subjects receiving placebo. Adherence was significantly ↓ in subjects taking 1200 mg/day dried cranberry juice vs those taking placebo
Saltzman et al.[62] (1994) ol	Community-dwelling elders aged ≥60 y (19)	1. 4 oz water 2. 4 oz cranberry juice (pH 2.5–2.6) 3. 4 oz 0.1 N HCl (pH 1.2)	Cranberry juice had NS effect on gastric pH at 1 + 2 h after administration. Did not affect oral vitamin B12 absorption

a Uroepithelial cells in all studies were obtained from healthy volunteers with no history of UTIs.

b 62% of UPEC strains were also resistant to cotrimoxazole.

bid = twice daily; **co** = crossover; **db** = double-blind; **NS** = not significant; **ol** = open-label; **r** = randomized; **SCI** = spinal cord injury; **tid** = three times daily; **UPEC** = uropathogenic *E. coli*; **UTI** = urinary tract infection; ↑ indicates increased; ↓ indicates reduced; → indicates followed by.

virulence of *E. coli* strains bearing P-fimbriae and/or type I pili but not strains lacking these two determinants.[57]

The high-molecular-weight fraction of cranberry dose-dependently inhibited the proteolytic enzymes produced by the oral pathogens *P. gingivalis*, *Tannerella forsythia* and *Treponema denticola*.[13]

The protective effect of cranberry juice on infection-induced oxidative renal damage in a rabbit model of vesico-ureteric reflux (VUR) has been evaluated. Rabbits were divided into five groups: group 1, sham-operated controls (n = 4); group 2, VUR with sterile urine (n = 8); group 3, VUR with UTI after instilling a P-fimbriated strain of *E. coli* (n = 8); group 4, same as group 3 but fed cranberry powder (1 g/kg/day) [n = 8]; and group 5, same as group 3 but given one intraperitoneal dose of melatonin 20 mg/kg (n = 8). Results were assessed via histology and quantitation of malondialdehyde (latter quantitates oxidative renal damage). At 3 weeks after creating VUR, rabbits were euthanized. The histological appearance of the renal tissues of groups 2, 4 and 5 was very similar, demonstrating a mild mononuclear infiltrate without fibrosis, while that of group 3 demonstrated severe damage, with periglomerular monocytic cell infiltration, tubular dilatation and atrophy, interstitial fibrosis, and occasional tubular inflammatory infiltrates and micro-abscesses (results were quantitated using a 0–3 scoring grid; $p < 0.05$). Malondialdehyde levels in renal tissue were significantly higher in group 3 rabbits compared with those in groups 1, 4 and 5 ($p < 0.05$). Also, levels did not differ significantly in groups 2, 4 and 5 rabbits. Results of this study suggest that cranberry may ameliorate UTI-associated renal damage in individuals with VUR.[58]

3.6 In Humans

The results of human pharmacodynamic studies (table III [28,30,32,38,43,45,46,49,56,59-62]) have generally corroborated those from *in vitro* and *in vivo* (animal) studies. Hippuric acid concentrations in urine, after single doses of cranberry juice cocktail of up to 4 L, rarely approached the lower limit

of bacteriostatic concentrations (0.020 mol/L). Ingestion of cranberry products had little or no effect on bacterial growth but did significantly reduce P-fimbriated uropathogen adherence to uroepithelium and silicone rubber in a dose-dependent manner. In addition, cranberry ingestion also reduced biofilm production. These results thus supported the clinical evaluation of cranberry products in the management of UTIs in humans.

4. Mechanism of Action

In summary, the following can be stated in terms of the mechanism(s) of action of cranberry in the prevention of UTIs. The hypothesis that cranberry works via urinary acidification (due to enhanced salicylate excretion and the metabolism of quinic and benzoic acids to hippuric acid *in vivo*) is not tenable. Individuals cannot ingest sufficient cranberry juice to generate sufficient hippuric acid to produce a bacteriostatic effect. In addition, non-antimicrobial urinary acidifiers such as ammonium chloride do not prevent UTIs.[2,18,19] The hypothesis that cranberry works via blockade of the adhesion of type I-fimbriated uropathogens to uroepithelial cells, which is mediated by its fructose content, similarly lacks support. No data exist that fructose alone works in this manner.[2,18,19]

The hypothesis that cranberry selects out less adherent uropathogens in the stool reservoir remains unproven.[2,18,19] The hypothesis that the total reducing capacity of cranberry constituents, including vitamin C, facilitates nonenzymatic generation of nitric oxide remains unproven.[63]

It does appear that the interaction of uropathogens with mucosal cells is mediated via a receptor containing D-mannose or a mannose-like structure. Both D-mannose and methyl γ-D-mannopyranoside (αMM) inhibit this adherence, while D-galactose, N-acetyl-D-glucosamine, wheat germ agglutinin and peanut agglutinin have no effect.[64] The inhibition of αMM is reversible and dose proportional (over a range of 2–6 mg sugar/mL. 100% inhibition occurs at 25 mg sugar/mL).[64] In fact, pre-attached *E. coli* can be displaced from their attachment sites on mucosal cells by D-mannose and αMM.[64]

In further studies, αMM did not affect the adherence of *P. mirabilis* 333 (a non-fimbriated bacterium) to mucosal cells. Methyl α-D-glucopyranoside (αMG) and L-fucose had no effect on the adherence of *E. coli*. During *in vivo* experiments in mice, intraperitoneal administration of αMM at the same time as bacterial inoculation significantly reduced urinary tract colonization with UPEC ($p < 0.0001$). Efficacy of αMM was dose-related, with three doses being more effective at reducing colonization rates than one dose ($p < 0.05$). In contrast, αMG had no effect on colonization with UPEC, while αMM was significantly more effective than αMG in reducing colonization rates ($p \leq 0.0001$). Histology of the urinary tract mucosa supported these findings.[65]

Thus, the major mechanism by which cranberry appears to prevent UTIs involves inhibition of the binding of the P-fimbriae of uropathogens via mannose-specific, lectin-like structures to mannose-like residues on mucosal cells. The precise effects of cranberry on the interaction of bacterial fimbriae with their mucosal receptors are not known. However, studies have established that cranberry reduces the strength of the binding between these two moieties and also alters the conformation of surface macromolecules (equilibrium length of P-fimbriae is shortened from 148 to 48 nm; i.e. proteins are more compressed).[66] The inhibition of P-fimbriae is felt to be irreversible.[31] In 100% inhibited bacteria, P-fimbriae cannot be seen by electron microscopy and such bacteria undergo elongation.[31] Whether or not P-fimbriae are removed under the influence of cranberry is controversial. Most investigators feel that the density of P-fimbriae is not affected by the presence of cranberry.[2,18,19]

Recently, a thermodynamic approach has been used to evaluate the interaction between bacteria and uroepithelial cells under the influence of cranberry juice (0–27 wt.%). The two organisms tested included *E. coli* HB101pDC1 (P-fimbriated) and *E. coli* HB101 (non-fimbriated). During the interaction of *E. coli* HB101pDC1 and uroepithelial cells, the change in Gibbs free energy of adhesion was always negative,

suggesting favourable adhesion and these values were insensitive to changes in cranberry juice concentration. For the fimbriated organism, the change in Gibbs free energy of adhesion became positive at a concentration of 27 wt.%, suggesting unfavourable adhesion. Bacterial adhesion (*E. coli* HB101pDC1) per uroepithelial cell was also assessed (for 0, 5, 10 and 27 wt.% concentrations, the mean ± SD numbers of bacteria per uroepithelial cell were 50.2 ± 22.9, 13.6 ± 5.7, 9.3 ± 4.1 and 2.9 ± 1.5, respectively). The correlation of number of adhered fimbriated *E. coli* versus change in Gibbs free energy was characterized by an exponential decay fit ($y = 4.748 + 0.04e^{-x/2.766}$, $r^2 = 0.99$). These data confirm that cranberry appears to disrupt bacterial ligand-uroepithelial cell receptor binding.[67]

Lastly, there is a paucity of data regarding the activity of cranberry against type I pili. However, the activity of cranberry against three strains of uropathogenic *E. coli* containing only type I pili (no P-fimbriae) has been clearly demonstrated. As for P-fimbriae, cranberry reduced the adhesion of these organisms to uroepithelial cells in a dose-dependent fashion.[37,61]

5. Pharmacokinetics

The pharmacokinetics of the cranberry plant must be described in terms of the pharmacokinetic parameters of the individual constituents. As there are literally hundreds of chemical constituents in natural products such as cranberry, this becomes an overwhelming task unless the active moiety/moieties can be identified in order to narrow down the possibilities.

Eleven healthy volunteers participated in a study of the urinary excretion of the anthocyanidins after ingestion of a single 200 mL dose of cranberry juice containing 651 mg of total anthocyanidins. Six of 12 anthocyanidins identified in cranberry juice were also seen in the urine, accounting for over 90% of total anthocyanidin urinary excretion (cyanidin 3-O-galactoside = 14.3% of total urinary anthocyanidins and 3.7% of the dose, cyanidin 3-O-arabinoside = 12.0% of total urinary anthocyanidins and 3.6% of the dose, peonidin 3-0-galactoside = 56.1% of total urinary anthocyanidins and 11.0% of the dose, peonidin 3-0-arabinoside = 14.1% of total urinary anthocyanidins and 2.0% of the dose, while the 3-O-glucosides of cyanidin and peonidin are minor urinary constituents). Pelargonidin and petuniden are very minor urinary constituents. Peak urinary anthocyanidin concentrations are seen 3–6 hours after intake and urinary excretion is nearly completed within the first 12 hours. Total urinary anthocyanidin recovery over 24 hours is approximately 5% of the dose.[26]

Of 14 phenolic acids and four flavonoids readily identified as constituents in cranberry products, only five of the phenolic acids and none of the flavonoids can be quantitated in plasma after administration in humans. These include benzoic, O-hydroxybenzoic, 2,3-dihydroxybenzoic, ferulic and sinapic acids. The benzoic acids can be measured only at 0.75 hours and 4.5 hours after administration, while ferulic and sinapic acids can be measured only at 4.5 hours after administration. In addition, two phenolic acids not seen in cranberry products can be identified in the plasma at 0.75 and 4.5 hours after administration: p-hydroxybenzoic and 2,4-dihydroxybenzoic acids. These acids may be metabolites of one or more of the phenolic acids native to cranberry.[22]

As salicylic acid is a constituent of cranberry juice, the pharmacokinetics of salicylate after cranberry ingestion have been evaluated in 22 healthy female volunteers. Cranberry juice was administered 250 mL three times daily for 14 days (daily salicylate ingestion = 5.25 mg compared with normal dietary salicylate ingestion of 10–200 mg daily). Compared with placebo in this crossover study, the urinary excretion of salicylic and salicyluric acids was significantly increased within 1 week of initiation (both $p < 0.001$) and continued to be elevated at the end of the study (both $p < 0.001$). Plasma salicylic acid concentration was significantly elevated at the end of the study ($p < 0.05$), although the absolute magnitude of the elevation was small (baseline = 0.00138 ± 0.00152 mg/dL → 0.00469 ± 0.00276 mg/dL).[23]

In an 8-week trial, 65 healthy female volunteers (aged 19–28 years) were randomized to

receive placebo (n = 23), dried cranberry juice 400 mg once daily (n = 20) or dried cranberry juice 400 mg three times daily (n = 22); 200 mg of this dried product (Nutri-Cran 90®) is equivalent to 5 g of fresh cranberries. Only in the 1200 mg/day group were there significant increases in a variety of urinary analytes (compared with placebo): hippuric acid, salicyluric acid and related isomers, quercetin glucuronide isomers and dihydroxybenzoic acid isomer (all $p < 0.05$).[32]

A recent review article[4] has provided an excellent summary of flavonoid pharmacokinetics. With these compounds, oral absorption is more efficient with the natural glycosylated forms as opposed to the aglycone (nonglycosylated) forms. The glycosylated forms compete with glucose for SGLT1 (intestinal sodium/glucose cotransporter). Only 5% of ingested flavonoids reach the circulation, the flavonol forms being able to do this most easily. Quercetin appears in the plasma in its glucuronidated or sulfated forms. Where this occurs is not known (gut wall vs hepatic first-pass). Flavonoids can re-enter the intestines via the transporter multidrug resistance protein (MRP)-2 and they are cleared from the circulation via MRP-3. Flavonoids not absorbed in the small intestine are subjected to microbial degradation in the colon. Flavonoids are difficult to quantitate in plasma after ingestion of cranberry products because of their tight binding to plasma proteins and red/white blood cell membranes. In contrast, free phenolic acids are much easier to quantitate in plasma after cranberry ingestion.[4]

At present, the relevance of the pharmacokinetic parameters of cranberry constituents with respect to efficacy and/or tolerability in UTI management is unknown.

6. Clinical Efficacy

All of the clinical data to be discussed herein involve the efficacy of cranberry products in the prevention of UTIs, defined clinically and/or in terms of laboratory test results (leukocytes, leukocyte esterase, nitrites, bacterial counts). There are no published data involving the use of cranberry products alone or together with antimicrobials in the treatment of UTIs. Results of an unpublished study of the treatment of six patients with UTIs with 12 capsules daily of cranberry juice concentrate 800 mg/capsule (Pharmacaps® brand) demonstrated no cures.[68] In the same study, this same regimen as prophylaxis in 21 subjects produced no UTIs in 20 subjects (95%).[68]

6.1 Prophylaxis in Adults

Moen[69] has reviewed his anecdotal experience with cranberry juice (two 6 oz glasses daily) in the management of recurrent frequency, dysuria and urgency in abacteriuric female patients, and in males with frequency after transurethral prostatic resection. The author also discussed his preliminary experience with cranberry juice therapy in patients with recurrent nephrolithiasis.[69]

Other authors have provided their anecdotal experience with cranberry products in patients post-renal transplant and those with neurogenic bladder dysfunction. Several hundred patients have received cranberry juice for UTI prophylaxis, usually administered as 200 mL twice daily. Taste, efficacy and tolerability have generally been described as good, with occasional complaints of gastrointestinal discomfort and the need for increased insulin dosage in those with diabetes mellitus. Three female renal transplant patients, each with an average 3–5 difficult-to-treat UTIs annually, had dramatic decreases in UTI incidence (to 0–1 event annually) after commencing cranberry prophylaxis. Persistent bacteriuria due to *E. coli*, *Proteus* spp., *Klebsiella* spp. and other organisms could not be cleared by the use of cranberry products. Cranberry products generally could not be used in patients with ileal conduits owing to intolerable irritation of the mucosa of urostomas.[70]

The results of open-label and randomized controlled trials of the prevention of UTI or colonization with cranberry products are presented in table IV.[68,71-84] Data for adults are presented in four groupings: adult women with recurrent UTIs, patients with neurological disease, the elderly and women during pregnancy.

Table IV. Clinical trials of cranberry products in the prevention of urinary tract infection (UTI) or colonization in adults and children

Study (year) and design	Population (no.)	Treatment	Results
Women with UTIs			
Walker et al.[71] (1997) r, db, pc, co	Women with recurring UTIs aged 28–44 y (19)	400 mg cranberry solids capsule[a] od × 3 mo and placebo od × 3 mo. Order of treatments was randomized. 6 mo study duration (no washout period between phases)	10 completed study (9 withdrew because of pregnancy, non-urinary infections requiring therapy, loss to follow-up). 21 UTIs occurred during the study in these 10 subjects. Only 2/21 UTIs (10%) were due to non-*Escherichia coli* bacteria. While on cranberry vs placebo, 7/10 subjects had fewer UTIs, 2 had the same number and 1 had 1 more UTI. Incidence rates for UTIs were 2.4/subject-year (cranberry period) and 6.0/subject-year (placebo period) [$p < 0.005$]
Kontiokari et al.[72] (2001) r, pg	Women who had been treated for a symptomatic UTI, [96.7% aged ≤55 y] (149)	Cranberry-lingonberry juice concentrate (containing 7.5 g cranberry concentrate and 1.7 g lingonberry concentrate in 50 mL) 50 mL/day × 6 mo (n = 50). *Lactobacillus* GG 100 mL/day (5 days/wk) × 1 y (n = 49). Untreated controls (n = 50). 1 y study duration	13 subjects prematurely discontinued study, in most cases due to moving away from the study site. During the initial 6 mo, 16%, 39% and 36%, respectively, of the cranberry-lingonberry, *Lactobacillus* GG and untreated control subjects experienced at least 1 UTI episode. In the cranberry-lingonberry group compared with the control group, this represented an absolute risk reduction of 20% (95 % CI 3, 36; $p = 0.023$, NNT = 5 [95% CI 3, 34]). After 12 mo, 24%, 43% and 38%, respectively, of the cranberry-lingonberry, *Lactobacillus* GG and untreated controls had experienced at least 1 UTI episode. It should be remembered that cranberry-lingonberry recipients had no active ingredient ingestion from mo 7 to 12. The cumulative first recurrence of UTI differed significantly between the groups throughout the study ($p = 0.048$ at 12 mo). Recurrence rates were significantly lower in the cranberry-lingonberry group compared with the untreated control group ($p = 0.014$ at 6 mo; $p = 0.052$ at 12 mo). During follow-up there were 98 UTI episodes (21, 39 and 38 occurring in the cranberry-lingonberry, *Lactobacillus* GG and untreated control groups, respectively). The difference of 0.36 in incidence densities per person-year between cranberry-lingonberry and untreated control groups was significant (95% CI 0.03, 0.68; $p < 0.05$). The proportions of UTIs caused by *E. coli* and women with positive perianal or urethral cultures for lactobacilli were similar in the groups. No AEs were reported except ''occasional complaints about the bitter taste of the cranberry juice''.
Stothers[73] (2002) r, sb, pc	Women with recurrent UTIs aged 21–72 y (150)	Cranberry juice (pure, unsweetened)[b] 250 mL tid (n = 50). Concentrated cranberry extract tablets (at least 1 : 30 concentrated juice)[b] bid (n = 50). Placebo (n = 50). 12 mo study duration	The proportions experiencing at least 1 UTI during treatment were 32% (placebo), 20% (juice; $p < 0.05$) and 18% (tablet; $p < 0.05$). The mean numbers of UTIs during treatment were 0.72 (placebo), 0.30 (juice; $p < 0.05$) and 0.39 (tablet; $p < 0.05$). AEs included headache and mild nausea (in 2 patients each) in the placebo group, GI reflux in 3 patients (2 of whom discontinued study participation) in the juice group, and mild nausea and increased frequency of stooling (in 4 and 1 patients, respectively) in the tablet group. 8 and 2 patients, respectively, complained about the size of the tablets and stated that they were difficult to swallow. The annual cost of prophylaxis was $US624 and $US1400 for the tablet and juice treatments. The average cost-effectiveness ratios for tablets and juice were $US1890 and $US3333 per UTI prevented
Bailey et al.[74] (2007) ol	Women with a history of ≥6 UTIs in previous year, aged 25–75 y (12)	Cranberry capsule (200 mg of extract, standardized to 30% phenolics)[c] bid × 12 wk	No UTIs occurred during the study (clinical, laboratory). 24 UTIs would have been expected based on the patients' prior history. No AEs were reported. At the 2 y follow-up, 8 patients had been taking cranberry supplements in doses of 150–300 mg/day (variety of suppliers). No

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Table IV. Contd

Study (year) and design	Population (no.)	Treatment	Results
			UTIs had occurred in these subjects and prodromal UTI symptoms could be alleviated by increasing cranberry and water intake temporarily. 4 patients stopped cranberry supplements for a variety of reasons. 1 patient remained UTI-free, 2 developed symptoms that resolved on resumption of the supplements and 1 developed a confirmed UTI, which was treated. The latter patient resumed supplement therapy after her antibacterial therapy was completed and has had no further problems
Patients with neurological disease			
McGuinness et al.[75] (2002) r, db, pc	MS patients with neurogenic bladder (135)[d]	8000 mg cranberry supplement capsule[e] od. Placebo od. 6 mo study duration	12 subjects did not complete study participation. 34.6% of cranberry and 32.4% of placebo recipients developed a UTI during the study (p = NS). Similar findings were noted for the 2 subgroups of users of ISC and non-users of ISC
Waites et al.[76] (2004) r, db, pc	Adults with SCI with neurogenic bladder and baseline pyuria with UC with $\geq 10^4$ cfu/mL (74)	Concentrated cranberry extract (capsule form)[f] 1 g bid (n = 36). Placebo bid (n = 38). 6 mo study duration	10 cranberry and 16 placebo recipients withdrew prior to study completion. Reasons included nonadherence, requirement for systemic antimicrobials for non-urinary infection, changes in bladder management and AEs (quantitative data NR). There were no significant intergroup differences in urinary bacterial counts $\geq 10^4$ cfu/mL, types and numbers of bacterial species, numbers of urinary leukocytes, urinary pH or episodes of symptomatic UTI
Linsenmeyer et al.[77] (2004) r, db, pc, co	Adults with SCI with neurogenic bladder (37)	Cranberry 400 mg tablet[g] tid × 4 wk and placebo tid × 4 wk. 1 wk washout phase between treatments. 9 wk study duration	16 patients withdrew prior to study completion (5 had recurrent UTIs, 3 had out-of-town travel, 6 had no specific reason and 1 each did not start the study or had an AE [abdominal discomfort]). There were no significant intertreatment differences in urinary pH, urinary bacterial counts, pyuria or urinary bacterial counts plus pyuria in combination. The identities of the treatments being received at the time of UTI recurrence (n = 5) were NR
Lee et al.[78] (2007) r, db, pc	SCI-associated neurogenic bladder (305)	MH 1 g bid (n = 75). Cranberry 800 mg[b] bid (n = 78). MH 1 g bid + cranberry 800 mg[b] bid (n = 75). Placebo (n = 77). 2 y recruitment period from 11/2000 and 6 mo follow-up	Patients on MH did not have a significantly longer time to symptomatic UTI vs placebo group (HR 0.96; 95% CI 0.68, 1.35; p = 0.75). Similar results were noted with cranberry (HR 0.93; 95% CI 0.67, 1.31; p = 0.70) and the combination of MH + cranberry (HR 0.93; 95% CI 0.56, 1.55; p = 0.91). AEs occurred in 14/305 (4.6%): diarrhoea or constipation in 11, nausea in 2 and rash in 1. AE rates were similar in the 4 groups
Hess et al.[79] (2008) r, db, pc, co	Adults with SCI with neurogenic bladder at a Veterans Affairs hospital (57)	Concentrated cranberry fruit extract (500 mg) tablet od[h] × 6 mo. Placebo od × 6 mo. Order of treatments was randomized. 6 mo study duration (no washout period between phases)	47 completed the study (1 died, 6 were non-adherent with study visits or assigned therapy, 2 developed urinary tract stones, 1 completed only initial 6 mo). During the study, 28 UTI episodes occurred in 22 subjects. Symptoms included sweating (in 21), bladder spasm (in 14), autonomic dysreflexia (in 11), fever (in 9), malaise (in 9) and abdominal discomfort (in 1). There was no significant difference in incidence of significant bacteriuria ($>10^4$ cfu/mL) between groups: 31 during cranberry phase, 37 during placebo phase. However, UTI incidence was significantly reduced during the cranberry phase (7/6 mo) compared with the placebo phase (21/6 mo) [p = 0.01]. Fewer subjects developed ≥1 UTI during the cranberry phase (13%) compared with the placebo phase (34%; p = 0.03). The incidence rate of UTI (prorated to 12 mo) during the 6 mo placebo phase (0.9/person-year) was not significantly different from the rate during the 1 y prior to the study (1.3/person-year; p = 0.07). In contrast, the corresponding incidence rates for the 6 mo cranberry phase were 0.3 and 0.9/person-year

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Table IV. Contd

Study (year) and design	Population (no.)	Treatment	Results
			(p = 0.01). Using logistic regression analysis, the OR for UTI during the cranberry phase was 0.3 (p = 0.01), suggesting a 70% reduction in the monthly likelihood of UTI during cranberry use. The likelihood of all symptoms except bladder spasms (p = 0.07) was also significantly reduced by cranberry use (all p < 0.05). By univariate analysis, there were 2 predictors of having a UTI: a history of UTI and the method of bladder management (descending order of UTI risk: indwelling catheter, intermittent straight catheter, condom catheter) [both p < 0.05]. Subjects with GFR >75 mL/min had an improved outcome: of the 22 subjects, 9 had 11 UTIs during the placebo phase but there were no UTIs during the cranberry phase (p < 0.01). Subjects with GFR <75 mL/min did not achieve significant benefit from cranberry (p = NS). By multivariate analysis, only treatment (cranberry) [OR 0.28] and history of UTIs (OR 2.2) were significant predictors of developing a UTI. No AEs were reported
Elderly			
Gibson et al.[68] (1991) ol	Residential care facility (11) and intermediate care facility (19) residents (elders)	4–6 oz daily of cranberry juice cocktail[i] × 7 wk	1 resident was discontinued because of consistent non-adherence; 2 residents died, 1 shortly after study began and the other at wk 4. 10 residents (33%) had negative LE and nitrites, <10 WBCs/HPF and <200 cfu on culture. 9 residents (30%) had trace (2+) LE, no nitrites, 6 WBCs/HPF and <200 cfu on culture. 9 residents (30%) had trace or greater LE, in most cases were nitrite-positive, numerous WBCs/HPF and >200 cfu on culture. UTI was defined as trace or greater LE and/or nitrites on the 3 dipstick tests, confirmed by microscopy and significant colony count on Unibac® plates (this is an atypical definition as signs/symptoms were not present). By this definition 10/30 (33%) did not have a UTI while on therapy. However, no baseline (pre-therapy) urine specimens were obtained, so nothing can be said regarding change from baseline
Avorn et al.[80] (1994) r, db, pc	Female assisted living (109) or nursing home (44) residents (elderly)	Cranberry juice cocktail[i] 300 mL/day (n = 72). Placebo (n = 81). 6 mo study duration	12 and 20 recipients of cranberry juice concentrate and placebo, respectively, withdrew early from the study (no details were provided). Cranberry recipients had a 58% reduction in the risk of significant bacteriuria (≥10^5 cfu/mL) with pyuria as compared with controls (OR 0.42; 95% CI 0.23, 0.76; p = 0.004). This relationship was not altered when a history of UTI in the previous 6 or 12 mo was added to the model (respective ORs were 0.53 [p = 0.049] and 0.48 [p = 0.01]). Cranberry recipients also had a 73% reduced risk of continuing bacteriuria/pyuria compared with controls (OR 0.27; p = 0.006). This relationship was also unaffected by adjusting for a history of UTI in the preceding 6 mo (OR 0.69; p = 0.02) or 12 mo (OR 0.30; p = 0.01). UTIs were uncommon, wherein only 4% of 473 cranberry and 7% of 498 control urine samples had bacteriuria and pyuria concurrent with urinary tract symptoms (p = NS). Urine pH was not significantly affected by either treatment. In an analysis of the 28 urine samples examined for their antiadhesive effect on *E. coli in vitro*, 13/13 urine samples collected during receipt of cranberry juice were found to inhibit *E. coli* adhesion. In contrast, 15/15 urine samples collected during receipt of placebo were devoid of such activity
McMurdo et al.[81] (2005) r, db, pc, pg	Hospitalized patients aged ≥60 y (376)	Cranberry juice cocktail (25% concentrated juice)[i] 150 mL bid	21/376 (5.6%) developed a symptomatic UTI (14/189 [7.4%] with placebo and 7/187 [3.7%] with juice; p = NS). Study durations in placebo and juice recipients were medians of 21 and 24

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Table IV. Contd

Study (year) and design	Population (no.)	Treatment	Results
		(n = 187). Placebo bid (n = 189). Treatment duration was 35 days or until hospital discharge, whichever came first	days, respectively. Duration of treatment consumption in placebo and juice recipients were medians of 15 and 16 days. There were no significant intertreatment differences in level of treatment adherence or frequency of antimicrobial use. AEs (13, 6 with placebo and 7 with juice) led to study discontinuation in all cases. The 6 AEs in the placebo group involved death in 2 and GI upset in 4. The 7 AEs in the juice group comprised death in 3, GI upset in 2, erythema and pruritus in 1 and hyperglycaemia in 1. Early study discontinuation occurred in 30% of enrolees (30% receiving placebo and 28% receiving juice). The most frequent reasons for discontinuation were desire to stop (13% with placebo and 12% with juice), dislike of beverage taste (7% and 6%) and need to perform urinary catheterization (6% and 4%). The frequency of *E. coli* on culture was significantly lower in placebo recipients (4) vs juice recipients (17; p = 0.027)
Pregnancy			
Wing et al.[82] (2008) r, db, pc	Pregnant women <16 wk gestation (188)	Low-calorie 27% cranberry juice concentrate 240 mL tid with meals. Same as above except 240 mL od at breakfast. Placebo. All regimens continued until delivery. The bid dosage groups (cranberry and placebo) were begun after 52 subjects had been enrolled (due to AE rates on tid regimen). Also, step-down from a bid to od regimen was allowed for moderate-severe GI disturbance	Outcomes of interest were UTI and asymptomatic bacteriuria. Of those completing the study 10 had taken cranberry od, 15 had taken cranberry tid, 47 cranberry bid and 43 placebo (total = 115). There were 4 UTIs (1 cystitis, 3 pyelonephritis) and 23 episodes of ASB. There were no significant intertreatment differences with regard to UTI and ASB frequencies. Adherence was a considerable obstacle during the trial, mandating changes in study design that became fatal flaws. Adherence rates (mean ± SD) were 66% ± 31%, 79% ± 29% and 77% ± 25% in the groups assigned to cranberry tid, cranberry od, and placebo, respectively (p = 0.03). 73/188 (39%) withdrew early, mostly because of GI upset, including nausea, vomiting, diarrhoea and taste dislike (44/73). Fewer premature withdrawals occurred after the dose changes were made (50/136, 37%) vs before (23/52, 44%; p = NS). No intertreatment differences were significant for obstetric or neonatal outcomes
Children with neurogenic bladder			
Foda et al.[83] (1995) r, sb, co	Children with neurogenic bladder managed with CIC of whom 12 continued prophylactic antibacterials (40)	Cranberry juice cocktail[i] 15 mg/kg/day × 6 mo and water × 6 mo. Divided into 4 doses/day. 12 mo study duration (no washout period between phases)	21 subjects completed the study. 12 withdrew for reasons related to cranberry (taste in 9, caloric load in 2, cost in 1), 7 for other reasons. The cranberry and water periods contributed 112 and 117 patient-months, respectively. There were no significant intertreatment differences in the proportions of patient-months with negative UCs (58.9% and 53.9%), patient-months with positive/significant UCs with UTI symptoms (17% and 17.1%) and patient-months with positive/significant UCs with no symptoms (24.1% and 29%). 9 patients each experienced more negative months while receiving cranberry juice and water compared with the other treatment and 3 patients experienced no difference between treatments (p = NS). Results were similar in recipients and non-recipients of antibacterial prophylaxis

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Table IV. Contd

Study (year) and design	Population (no.)	Treatment	Results
Schlager et al.[84] (1999) r, db, pc, co	Children with neurogenic bladder undergoing CIC [myelomeningocele] (15)	Cranberry concentrate 2 oz od (equal to 300 mL of cranberry juice cocktail)[i] × 3 mo and placebo × 3 mo 6 mo study duration (no washout period between phases)	There were no significant intertreatment differences in urinary pH and in the frequencies of significant bacteriuria ($\geq 10^4$ cfu/mL), symptomatic UTIs and isolation of *E. coli*. No AEs were reported

a Solaray® brand.
b Product not identified.
c Cranberry Supreme®.
d Numbers randomized to each group were not provided.
e NOW Natural Foods® brand.
f CranVerry®.
g Nature's Way®.
h Cran-Max®.
i OceanSpray®.

AE = adverse event; **ASB** = asymptomatic bacteriuria; **bid** = twice daily; **cfu** = colony-forming units; **CIC** = clean intermittent self-catheterization; **co** = crossover; **db** = double-blind; **GFR** = glomerular filtration rate; **GI** = gastrointestinal; **HPF** = high power field; **HR** = hazard ratio; **ISC** = intermittent straight catheterization; **LE** = leukocyte esterase; **MH** = methenamine hippurate; **MS** = multiple sclerosis; **NNT** = number needed to treat; **NR** = not reported; **NS** = not significant; **ol** = open-label; **od** = once daily; **OR** = odds ratio; **pc** = placebo-controlled; **pg** = parallel-group; **r** = randomized; **sb** = single-blind; **SCI** = spinal cord injury; **sign.** = significant; **tid** = three times daily; **UC** = urine culture; **WBC** = white blood cell.

In the largest and best quality randomized controlled trial in the elderly, the intergroup differences in the overall rates of symptomatic UTI were not significant. On *ad hoc* analysis, there was a significant reduction in the rates of *E. coli* UTIs in cranberry versus placebo recipients ($p = 0.027$) but caution is warranted based on the exploratory nature of the analysis.[81] In the second randomized controlled trial in the elderly, the intergroup differences in bacteriuria/pyuria rates in patients reporting urinary symptoms were also not significant. Caution is warranted in interpreting this trial because of discrepancies in data found in the abstract[85] and final report.[80] Further information regarding these findings were not forthcoming from the authors. In none of the four randomized controlled trials conducted in patients with neurogenic bladders were any of the intertreatment differences in symptomatic UTI rates statistically significant.[86,87] However, in a recent trial in the same population, cranberry tablets were found to be both significantly and nonsignificantly associated with reduced rates of development of significant bacteriuria, UTIs and UTI symptoms, depending on the statistical methods chosen.[79] In addition, cranberry had no significant effect on asymptomatic bacteriuria or UTI rates during pregnancy.[82]

6.2 Prophylaxis in Children

In two randomized, controlled trials involving children requiring intermittent catheterization because of spinal cord disease, there were no significant intertreatment differences in the rates of asymptomatic bacteriuria or UTIs (table IV).[83,84]

Investigators who were interested in the potential of cranberry as a prophylactic agent in UTIs in children wished to assess the tolerability of the liquid cocktail formulation in children as well as whether it would produce any deleterious effects on bacterial flora outside the urinary tract. In response, a randomized, double-blind, placebo-controlled trial was conducted in 341 children attending daycare centres (mean age 4.3 years). The aim of the study was to evaluate the effect of cranberry juice cocktail (OceanSpray® brand) ingestion on nasopharyngeal and faecal flora as

well as the epidemiology of infections (overall, respiratory, enteric). Subjects were randomized to receive either cranberry juice cocktail 1.67 mL/kg/day (maximum 300 mL/day) [n = 171] or placebo (n = 170) for 3 months. Premature study discontinuation rates were 11% (cranberry group) and 7% (placebo group). The major reasons for premature discontinuation were refusal to drink the beverage (6 placebo/4 cranberry), parents became tired of the study (3/7), rash (1/0), gastric symptoms (0/2), illness during the trial (1/2) and unknown (0/3). There were no significant intra- or intergroup differences in the nasopharyngeal carriage of respiratory pathogens. As measured by bacterial fatty acid composition, faecal flora significantly changed in both groups over time (both $p < 0.001$) but the intergroup differences were not significant. There were also no significant intergroup differences in overall infection episodes (number or duration), respiratory tract infections or enteric infections. Similar findings were noted for frequencies of possible bacterial and viral infections, and three of the four most common paediatric infections. Only for conjunctivitis was there a significant intergroup difference: 0.1 and 0.4 diagnoses per person-year at risk in the placebo and cranberry groups, respectively ($p = 0.05$). Thus, cranberry juice cocktail was well tolerated and did not affect bacterial colonization and infection epidemiology in a paediatric population.[88]

Utilization of cranberry products by paediatric prescribers and paediatric nephrology clinic patients has been the subject of two surveys.[89,90] A survey was conducted of 169 spina bifida clinics in the US and 59 (39%) clinics returned the survey. Fifty-seven percent of respondents recommended cranberry or lingonberry juice/extracts to their patients to prevent UTIs, while only 50% believed that these products were of benefit.[89]

Between 1 June 2004 and 13 August 2004, parents of 117 paediatric nephrology clinic patients were surveyed about their beliefs and practices regarding cranberry use in their children. Mean patient age was 10.3 years and 65% were taking prophylactic antimicrobials. Recurrent UTIs were reported as problematic in 15%. Cranberry juice was used in 32 of 34 (94%) patients and pills/tablets/capsules and dried berries were used in 2 of 34 (6%) patients each. The most frequently used dosage regimen for the juice formulation was 1 cup once daily (range half cup to >1 cup from once to >3 times daily). Twenty-nine percent of parents administered cranberry products to prevent recurrent UTIs, treat UTIs and for other reasons in 7, 11 and 16 patients, respectively. Use was significantly more frequent among patients with recurrent UTIs (65%) compared with other renal disorders (23%, odds ratio 6.1; 95% CI 2.0, 18.4; $p < 0.001$). Cranberry was felt to have provided a cure, been very beneficial, been somewhat beneficial and to have had a neutral effect in 1, 20, 4 and 4 patients, respectively. Only one parent reported an adverse event (nausea). Only 23% of parents had discussed the use of cranberry products with their children's physicians. Only 40% of parents had been advised by health professionals to use cranberry products. Most parents used cranberry products only when their children were symptomatic. Approximately 50% of parents felt that cranberry plus antimicrobials was more effective than either agent as monotherapy. Among the 83 parents who had not given cranberry to their children, the most frequent reasons were lack of knowledge about it (36%), feeling that it would not help (24%) and the child's dislike of its taste (16%).[90]

6.3 Meta-Analyses

Clinical trials have generally been of poor quality. Groups have been small and randomization schemes have been unbalanced or poor. Most have lacked a power analysis to calculate sample size in order to avoid type 2 (false-negative) statistical error. Studies have been of too short a duration (<6 months). Studies have not assessed adherence with therapy in an objective manner (e.g. by measuring urinary output of proanthocyanidins or other unique markers of cranberry). Withdrawal rates have been as high as 47%. Children, in particular, have cited taste of the juice as the main reason for stopping therapy. However, withdrawal rates have also been high (>40%) in two randomized, controlled trials using cranberry capsules/tablets, so changing the

formulation may not solve the problem.[86] Dosages of cranberry juice or powdered extracts in capsule form have been quite heterogeneous. Studies have not attempted to establish whether or not a dose-response relationship exists for efficacy and/or tolerability. No systematic evaluation of the frequency of dose administration has been performed. Many studies have not used cranberry products that have constituents that are well characterized, quantified and standardized. Formal assessment of patient acceptability has been infrequently done. This is important for products with taste and caloric load issues as well as potential inconveniences such as the need to carry around liquid formulations if twice- or, especially, thrice-daily administration is deemed necessary. Lastly, next to nothing is known regarding the pharmacokinetics of the proanthocyanidins and other cranberry-derived compounds, and studies have not tested specific key cranberry-derived compound(s) that are considered likely to be the active moiety/moieties.[2,19,91]

Results of a Cochrane Database meta-analysis of cranberry efficacy in the prevention of UTIs were published in 2004. All randomized or quasi-randomized controlled trials of cranberry products in the prevention of UTIs in men, women and children were eligible for review. Seven trials met the inclusion criteria (four being crossover, three being parallel group). The effectiveness of cranberry (or cranberry-lingonberry) juice versus placebo juice or water was evaluated in six trials. The effectiveness of cranberry tablets/capsules versus placebo was evaluated in two trials (one trial evaluated both juice and tablets/capsules). In two good-quality randomized. controlled trials, cranberry products significantly reduced the incidence of UTIs at 12 months (relative risk [RR] 0.61; 95% CI 0.40, 0.91) compared with placebo/control in women. One trial used 7 g of cranberry concentrate daily in 50 mL and the other used 1 : 30 concentrate given either in 250 mL juice or in tablet form. There was no significant difference in the incidence of UTIs between juice and capsule formulations (RR 1.11; 95% CI 0.49, 2.50). Five trials could not be included in the meta-analyses owing to methodological flaws or lack of available data. Only one of these five trials reported a significant result for the outcome of symptomatic UTIs. Adverse drug events were common in all trials (rates up to 30%) and withdrawal rates in several of the trials were high (rates up to 48%). On the basis of this meta-analysis, there was some evidence that cranberry juice may reduce the frequency of symptomatic UTIs over a 12-month period in women. Whether it is as effective in children as it is in the elderly is not clear. The large number of withdrawals from some of the trials suggests that cranberry juice may not be acceptable over long periods. The optimum dosage or dosage formulation was also not clear.[92]

Two of the authors repeated a meta-analysis of identical design, the results of which were published in 2007. Nine trials met inclusion criteria (n = 1011 participants randomized to control or treatment). Of these, one was published as a letter to the editor and no additional data were provided by the authors. Seven trials had one intervention arm and one control arm, and evaluated the effectiveness of either cranberry juice (four trials) or cranberry capsules (three trials). Two further trials had two intervention arms (with randomization to either cranberry-lingonberry juice, *Lactobacillus* GG or no intervention, or cranberry juice, cranberry tablets or placebo juice). Three trials were excluded from further review because they did not measure any relevant outcome (two trials) or measured only asymptomatic bacteriuria (one trial). The study populations were varied. Three trials evaluated women with recurrent UTIs, two evaluated elderly subjects, and four evaluated subjects requiring indwelling urinary catheters or clean intermittent self-catheterization (all subjects in the four latter trials had neurogenic bladders). The rationale underlying the dosage of cranberry product used was not provided in any trial. Withdrawals occurred in all but one trial, and rates ranged from 8% to 55%.[86]

Relative risks of symptomatic UTIs could be calculated for four trials. The overall relative risk was 0.65 (95% CI 0.46, 0.90) [i.e. a 35% reduction in risk]. For the five trials not included in this analysis, only one reported a significant benefit of cranberry (i.e. 6 incidents in the cranberry arm vs 15 in the placebo arm; $p < 0.05$). When evaluating

the effectiveness of cranberry products in women with recurrent UTIs, data for meta-analysis were available from two randomized controlled trials (see the discussion of these under the 2004 meta-analysis[92]). In the third trial in women with recurrent UTIs, there were 21 UTI incidents among the 10 subjects completing the trial: 6 in cranberry recipients and 15 in placebo recipients ($p < 0.005$).[86]

In the most recent update of the Cochrane Database meta-analysis from 2008, ten studies met inclusion criteria (n = 1049 participants randomized to control or treatment). The juice formulation was used in seven studies and the tablet formulation in four (in one study, both formulations were evaluated). Cranberry products significantly reduced UTI rates in females at 12 months (RR 0.65; 95% CI 0.46, 0.90) compared with placebo/control. Efficacy in elderly men or women or those requiring intermittent catheterization could not be demonstrated. Six studies could not be used because of either methodological issues or lack of data. As in previous meta-analyses, the use of cranberry products was not recommended by the authors. The optimum dosage and formulation were still considered to be unclear. Further properly designed studies measuring relevant outcomes were advised before recommendations regarding cranberry use could be made.[87]

7. Tolerability

Few data are available specifically regarding the tolerability profile of cranberry products in humans. Some data are available from trials where tolerability was not the primary goal. For example, in a trial examining the effect of cranberry ingestion on urine composition, four healthy male volunteers ingested up to 600 g/day of cranberries (100–200 g with each meal). No discomfort was noted in any of the four volunteers, even at the highest dosage of 600 g/day.[55] In an 8-week trial in 65 healthy volunteers where the effects of ingestion of 400 and 1200 mg/day of dried cranberry juice on urine composition were evaluated, 57 subjects completed participation. Premature discontinuation because of ADRs occurred in two placebo recipients and six recipients of 1200 mg dried cranberry juice/day. The ADRs leading to discontinuation in the latter group included excessive urination and stomach acidity. All biochemical changes in all three groups were consistent with physiological variability.[32]

Because of the rich antioxidant content of cranberry, a study of the neurocognitive effects of cranberry juice cocktail was conducted in 50 cognitively intact elders aged at least 60 years with no significant history of neurocognitive impairment. In this 6-week randomized, double-blind, placebo-controlled trial, cranberry recipients received 32 oz of the OceanSpray® product (27% pure juice v/v). Nonsignificant differences occurred in the two groups in terms of subjective effects on a follow-up self-report questionnaire and quantitative neurocognitive testing (Selective Reminding Test, Wechsler Memory Scale-III Faces I and Faces II subtests, Trail Making Tests A + B, Stroop Color and Word Test, and Wechsler Adult Intelligence Scale [WAIS]-III Digit Symbol-Coding subtest).[93]

One well documented case of immune-mediated thrombocytopenia has been reported in a 68-year-old man who had ingested an unknown amount of juice for symptomatic relief of discomfort from an indwelling urinary catheter over the 10 days prior to admission. Admission platelet count was profoundly reduced from normal (to 1×10^9/L). The patient had experienced a 24-hour history of haematuria, oral petechiae, bleeding gums and skin bruising. Concurrent low-dose aspirin prophylaxis was discontinued and the patient received intravenous corticosteroid and immunoglobulin (Ig)G therapies. The platelet count rebounded to 12×10^9/L by day 3 and 200×10^9/L by day 8. Corticosteroid doses were tapered over 6 weeks and a normal platelet count was maintained over the subsequent 18 months. A local poison control centre commented that cranberry juice can have traces of quinine in it, but subsequent investigations found no quinine-dependent antiplatelet antibodies. However, when evaluating dialyzed samples of the cranberry juice that the patient had ingested, serum cranberry juice-dependant IgM and IgG antiplatelet antibodies were found. The

specific platelet glycoprotein antigen specificity of the cranberry juice-dependent IgM/IgG antibodies could not be identified.[94]

Because of the effects of cranberry juice on the composition of urine, concern has arisen with respect to the risk of nephrolithiasis during therapy. Four studies have evaluated this toxicity potential. In one study, 12 healthy male volunteers aged 18–38 years received a standard diet and were treated with four consecutive 5-day regimens: 330 mL daily of water (placebo), plum juice, cranberry juice and blackcurrant juice. With cranberry juice compared with placebo, urinary pH fell, oxalic acid output rose, and relative saturation of uric acid rose (all $0.01 < p < 0.05$). With blackcurrant juice compared with placebo, pH rose, citric acid output rose (both $0.001 < p < 0.01$) and oxalic acid output rose ($0.01 < p < 0.05$). Plum juice had no significant effect on any urinary parameter. It was concluded that blackcurrant juice may play a role in the treatment of urate nephrolithiasis because of its alkalinizing effect. Cranberry juice may enhance the risk of urate stones but may play a role in the treatment of apatite, brushite and struvite nephrolithiasis.[95]

The second study evaluated the effect of cranberry juice on urinary risk factors for calcium oxalate nephrolithiasis. Twenty healthy male volunteers drank 2 L of water daily for 14 days and 0.5 L of cranberry juice (diluted to 2 L with water) daily for 14 days. Each ingestion was separated by a 14-day washout period. Cranberry juice ingestion reduced mean oxalate excretion by 31% ($p < 0.001$), calcium excretion by 30% ($p = 0.0031$), phosphate excretion by 24% ($p = 0.0139$) and relative supersaturations of calcium oxalate (by 66%; $p < 0.001$), brushite (by 64%; $p < 0.001$) and uric acid (by 54%; $p < 0.001$). In contrast, citrate excretion rose by 31% ($p = 0.001$). Other urinary parameters were not significantly affected. Three changes that occurred with cranberry juice treatment alone (i.e. did not also occur with water treatment) included reductions in oxalate and phosphate excretion and enhancement of citrate excretion. In this study, cranberry juice appeared to be antilithogenic.[96]

The third study enrolled 12 healthy volunteers and 12 patients who were known calcium oxalate stone-formers. Beverages ingested included water and cranberry juice, 1 L daily of each for 7 days. Because of the similarity in results, data from the two groups were pooled. Cranberry juice significantly increased mean urinary calcium excretion (by 15%; $p = 0.0008$) and urinary oxalate excretion (by 11%; $p = 0.04$) and thus relative saturation for calcium oxalate (by 20%; $p < 0.01$). Urine pH fell by a mean of 0.30 units ($p = 0.0007$). Urinary ammonium, titratable acidity and net acid excretion were all increased (by 17%, $p = 0.006$; by 12%, $p = 0.007$; and by 20%, $p = 0.002$, respectively). Mean urinary uric acid excretion fell significantly (by 19%; $p < 0.0001$) as did serum uric acid concentration (by 8%; $p = 0.0003$). Urinary citrate excretion exhibited no change. Relative saturation for brushite and urate were reduced by cranberry juice (by 23%; $p = 0.02$ and 39%; $p = 0.009$, respectively) while the amount of undissociated uric acid was increased (by 26%; $p = 0.02$). Hence, this study found that cranberry juice had modest effects at most and did increase the risk of calcium oxalate and urate nephrolithiasis, but decreased the risk of brushite nephrolithiasis.[97]

The fourth study evaluated the effect of cranberry concentrate tablets on urinary risk factors for nephrolithiasis in five healthy volunteers (two female) treated for 7 days at the manufacturer's recommended dose. Twenty-four-hour urine collections were performed at baseline and on the day after completion of the 7-day cranberry regimen. The only significant differences from baseline to post-cranberry treatment involved urinary oxalate output (rose mean 43.4%; $p = 0.01$), sodium output (rose mean 41%; $p = 0.03$), magnesium output (rose mean 47.3%; $p = 0.02$), potassium output (rose mean 67.5%; $p = 0.006$) and calcium oxalate supersaturation (rose mean 50.7%; $p = 0.03$). Thus, cranberry concentrate tablet ingestion led to significant increases in the urinary excretion of two potential lithogenic agents (oxalate, sodium) and two inhibitors of stone formation (magnesium, potassium). In this study, cranberry concentrate was found to possibly enhance the risk of oxalate stones.[98]

The following can be deduced from these four preceding studies. Cranberry ingestion led

to a fall in urine pH in two studies (50%). Oxalate urinary output rose in three studies (75%) and fell in one. Calcium urinary output rose and fell in one study each (25%). Phosphate and uric acid urinary excretion fell in one study each (25%) and citrate urinary output rose in one study (25%). The relative supersaturation of uric acid rose in one study (25%) and fell in two (50%). The relative supersaturation of calcium oxalate fell in one study (25%) and rose in two (50%). The relative supersaturation of brushite fell in two studies (50%). None of these statistically significant changes appeared to be dose related, at least over a dosage range of 330–1000 mL of juice daily. The conclusions of the authors of each article with respect to the clinical impact of cranberry therapy varied substantially. One study suggested an increased risk of urate stones, but a decreased risk of brushite, apatite and struvite stones. Another article suggested an antilithogenic effect, and another suggested an increased risk of calcium oxalate and urate stones, but a decreased risk of brushite stones. Lastly, one study suggested a possible increase in the risk of calcium oxalate stones. At present, it is difficult to draw any conclusions from existing data. However, it would probably be prudent to avoid cranberry therapy in those with known nephrolithiasis. In addition, some authors feel that cranberry therapy is relatively contraindicated in the presence of renal impairment.[99]

In a systematic review of the literature, no direct evidence of safety or harm to the mother or fetus as a result of cranberry consumption during pregnancy could be found.[100] Indirectly, reasonable scientific evidence is available to suggest that cranberry may be of minimal risk.[101] In lactation, the safety or harm of cranberry juice is unknown.[100]

8. Drug Interactions

Flavonoids, which are major constituents in cranberries, have well known effects on cytochrome P450 (CYP) drug-metabolizing enzymes. They can induce the biosynthesis of several CYP isoenzymes, inhibit/stimulate the enzymatic activities of CYP isoenzymes and are metabolized by several CYP isoenzymes.[102] Table V illustrates flavonoids and their effects on various CYP isoenzymes.[102] In addition, flavonoids can affect phase II (synthetic) drug-metabolizing enzymes. For example, flavonone and flavone enhance the activities of glutathione-S-transferase and uridine diphosphate-glucuronosyl-transferase while quercetin and tangeretin do not.[102] Flavonoids are also aromatase inhibitors, aromatase being the crucial enzyme in estrogen biosynthesis. Some resemble the estrogens in structure and can have estrogenic or antiestrogenic activities (most natural flavonoids are not potent in these activities).[102]

Flavonoids in the diet are metabolized by colonic flora (glycosides are cleaved to free flavonoids or aglycones), with subsequent absorption of the glycosides and aglycones. Flavonoids during passage through the liver are hydroxylated and/or demethylated (phase I oxidation mediated by CYP isoenzymes). These metabolites then are subjected to conjugation (glucuronidation, sulfation and *O*-methylation). The

Table V. Activities of flavonoids on cytochrome P450 (CYP) isoenzymes[102]

CYP isoenzyme type	Type of activity		
	agonist/inducer	antagonist	no effect
1A1	Quercetin	Quercetin	Genistein
	Galangin	Kaempferol	Equol
	Diosmin	Galangin	Prenylchalcones
	Diosmetin		Prenylflavonones
	Tangeretin		
	Flavone		
	β-Naphthoflavone (apigenin)		
1A2	Flavone		Genistein
	Tangeretin		Equol
	β-Naphthoflavone		
2B1/2B2	Flavonone		
	(flavone)		
	(tangeretin)		
3A4	Flavone	Naringenin	
	Tangeretin	Bergamottin	
		Flavolignan	
		Sylimarin	
		Biapigenin	
		Hyperforin	

flavonoid skeleton degrades in the gut, facilitated by bacterial ring scission. Some examples of metabolism of flavonoids include:

- galangin → kaempferol → quercetin (mediated primarily by CYP 1A1)
- genistein → orobol (mediated by CYP isoenzymes 1A1, 1A2, 1B1, 2E1).

Of interest, naringenin is not metabolized via any CYP isoenzyme.[102]

Evaluating the effect of cranberry juice on the activity of CYP3A4 is important, since other fruit juices (grapefruit, Seville orange, pomegranate and pomelo juice) inhibit CYP3A4 in the wall of the gastrointestinal tract. Pre-incubation of human hepatic microsomes and rat small intestinal microsomes in the presence of 10% (v/v) cranberry juice produced significant reductions in the activity of nifedipine oxidase (CYP3A4). These mean reductions were in the order of 18.2% and 12.6%, respectively. Corresponding mean reductions by grapefruit juice (positive control) were 67% and 58.8%.[103] The interaction of cranberry juice and nifedipine was evaluated in rats: 2 mL of cranberry juice administered intraduodenally 30 minutes before administration of nifedipine 30 mg/kg produced a mean 1.64-fold increase in nifedipine area under the serum concentration-time curve (AUC) [mean 39% reduction in apparent oral clearance]. In comparison, grapefruit juice produced a mean 1.61-fold increase in nifedipine AUC and 44% reduction in apparent oral clearance. Other pharmacokinetic parameters (mean residence time, volume of distribution, elimination rate constant, peak concentration [C_{max}] and time to peak concentration) were not significantly altered. These results suggest that cranberry juice may only inhibit enteric CYP3A4 activity. Perhaps this is because the entity in cranberry juice that inhibits CYP3A4 activity cannot be absorbed and hence affect hepatic CYP3A4 activity. This effect is not due to furanocoumarins (the interacting substances in grapefruit juice); the anthocyanidins are the currently hypothesized interacting substances in cranberry.[103]

Twelve healthy male volunteers participated in a randomized, placebo-controlled, three-way crossover study of the effect of cranberry juice and pomelo juice on oral ciclosporin pharmacokinetics. Volunteers received single oral 100 mg doses on three occasions (with 240 mL of water [control], pomelo juice and cranberry juice) with 2-week washout periods between. Pomelo juice was prepared from the fruit and cranberry juice was obtained by reconstitution of frozen OceanSpray® concentrate on each administration day. Pomelo juice coadministration resulted in significant increases in mean whole blood ciclosporin AUC (both AUC to the last quantifiable drug concentration and from zero to infinity) and C_{max} by 19.4%, 18.9% and 12.1%, respectively ($p = 0.0001$, $p = 0.0001$ and $p = 0.0167$). However, only the increase in AUC could be considered clinically significant. These results were consistent with enhanced bioavailability due to inhibition of CYP3A4 and/or P-glycoprotein in the gut wall. Coadministration of cranberry juice resulted in a statistically significant (but not clinically significant) mean 6.6% reduction in AUC ($p = 0.0054$).[104]

In vitro and *in vivo* studies were conducted evaluating the interaction of the NSAID flurbiprofen (a substrate for CYP2C9) with cranberry juice, grape juice, tea and fluconazole. *In vitro*, 2.5% tea, 2.5% grape juice (Welch's® 100% pure juice), 2.5% cranberry juice (OceanSpray® cranberry juice cocktail, 27% pure juice), 2.5% cranberry juice placebo and 2.5 μmol/L sulfaphenazole reduced flurbiprofen hydroxylation to (mean ± SD) 11% ± 8%, 10% ± 7%, 56% ± 16%, 85% ± 5% and 21% ± 6% of control, respectively (all $p < 0.01$). Fourteen healthy volunteers then participated in a five-way crossover trial using single oral doses of flurbiprofen 100 mg. Cranberry juice placebo beverage (8 oz), cranberry juice (8 oz), tea (8 oz), grape juice (8 oz) and fluconazole (200 mg) were administered the night before and 30 minutes prior to morning flurbiprofen administration. All phases were separated by at least a 1-week washout period. Only fluconazole exerted a significant effect on flurbiprofen pharmacokinetics, with increases in C_{max}, elimination half-life ($t_{½}$) and AUC, and a decrease in apparent oral clearance (all $p < 0.05$).[105]

The effects of cranberry juice on the activities of CYP 2C9, 1A2 and 3A4 have been evaluated in

healthy volunteers through the use of the probe drugs warfarin (10 mg), tizanidine (1 mg) and midazolam (0.5 mg). Ten volunteers were randomized to cranberry juice or water (200 mL) three times daily for 10 days, receiving the probe drugs on day 5 followed by blood sampling for drug concentrations and thromboplastin time. Subjects then crossed over to the alternative treatment for 10 days and the same protocol was followed. The cranberry juice was prepared from concentrate and diluted 1 : 4 (v/v). Cranberry juice had no significant effect on C_{max}, AUC or $t_{½}$ (except *S*-warfarin for the latter) of any of the probe drugs and did not alter the thromboplastin time response to warfarin. The only significant effect of cranberry juice was a reduction in the $t_{½}$ of *S*-warfarin from a mean of 40.3 to 36.4 hours ($p < 0.05$). Results of this experiment suggest that cranberry juice does not adversely affect the activities of CYP1A2 and 3A4 in humans.[106]

Four reports of an interaction between cranberry juice and warfarin have been published.[107-110] Increases in international normalized ratio (INR) of prothrombin time to values of 6.5, 12, >18 and >50 were reported in these patients, with one patient dying as a result of gastrointestinal and pericardial haemorrhage.[107] Other reports summarized 12 cases reported to the Committee on Safety of Medicines (UK).[111,112] Eight patients experienced increases in INR with/without haemorrhage, three experienced unstable INR values and one involved a reduction in INR. Individuals ingested up to 2 L of juice per day. Potential mechanisms of this interaction included the salicylate content of the juice and the presence of CYP enzyme-inhibiting flavonoids.

Seven patients with atrial fibrillation (aged 68.8 ± 10.0 [mean ± SD] years) who were taking stable warfarin dosage regimens ingested 250 mL of cranberry juice daily for 7 days then placebo beverage for 7 days or vice versa. A 1-week washout period separated study phases. At all ten data points, there were no significant intertreatment differences in INR values.[113] These results plus results of studies evaluating the effect of cranberry juice on substrates of CYP2C9 (the enzyme that metabolizes warfarin)[105,106] suggest that the potential for a cranberry juice-warfarin interaction is low. However, in these studies the 'dose' of cranberry juice was reasonably low (240–250 mL of diluted [1 : 4] concentrate or cranberry juice cocktail). The effect of more than 1000 mL per day has not been evaluated.

In contrast to the previous study, another placebo-controlled study investigating the pharmacokinetic and pharmacodynamic interaction potential between cranberry and warfarin found that cranberry increased sensitivity to the dynamic effects of warfarin. Volunteers were pretreated with GNC brand cranberry juice concentrate capsules (two capsules three times daily, equivalent to 57 g fruit daily) for 14 days. Cranberry was also continued for the 7-day blood sampling period after a single 25 mg dose of warfarin. Volunteers (7 Caucasian, 5 Asian) were also genotyped for two major warfarin-metabolizing enzymes: CYP2D6 and vitamin K epoxide reductase complex subunit 1 (VKORC1). The CYP genotypes were *1/*1 (in 9) and *1/*2 (in 3). In terms of VKORC1, four had VKORC1 wild-type (CC) and eight had variant alleles (6 with CT, 2 with TT). Cranberry administration significantly increased the mean area under the INR time curve by 28% (10 of 12 [83%] had an increase in INR with cranberry use). The change in maximum INR level reached was not significant. There were also nonsignificant trends to greater reductions in the activities of factors II, VII and X with cranberry use. Platelet aggregation was not affected by cranberry use. Pharmacokinetic parameters for the *R*- and *S*-enantiomers of warfarin were not significantly affected by cranberry use. Pharmacodynamic-pharmacokinetic co-modelling revealed that cranberry use significantly increased sensitivity to the effect of *S*-warfarin (i.e. the plasma concentration producing 50% of the peak effect [EC_{50}] for *S*-warfarin fell from 443 ± 212 [SD] ng/mL to 376 ± 184 ng/mL with cranberry use). A genotype-specific interaction was also found. When warfarin and cranberry were coadministered, the *S*-warfarin EC_{50} values of the CT and TT alleles were reduced significantly more than that of the CC genotype (both $p < 0.03$). Results of this study suggest that a potentially clinically important

drug-drug interaction exists between cranberry and warfarin.[114]

In summary, *in vivo* studies in humans do not support any clinically important pharmacokinetic drug-drug interactions between whole cranberry and drugs that are substrates for CYP 2C9, 1A2 and 3A4. However, a clinically important pharmacodynamic interaction may occur between cranberry juice concentrate capsules (GNC brand, two capsules three times daily) and warfarin. Whether this interaction involves other formulations of cranberry is not known. Also, the effect of purified proanthocyanidins on drug metabolism is not known. Such information will become more important if administration of the active moiety of cranberry becomes a reality over time.

9. Dose Administration

Dose administration recommendations of cranberry products in the prevention of UTI have been poorly defined. Available products include beverage and solid dose (dried cranberry extract) formulations. The best studied of the beverage formulations is sweetened cranberry juice cocktail (OceanSpray®), which is approximately 25% pure juice. Recommended doses have ranged from 4 to 32 oz/day (in divided doses three times daily with meals).[99,115] Recommended doses of the dried concentrated juice extract (in capsule form) range from 600 to >1200 mg/day (in divided doses two or three times daily).[99,115] An important potential liability of the capsule formulations is the sensitivity of the dried cranberry extract contents to breakdown by exposure to light, heat and cold, although addition of vitamins E and C exerts a stabilizing influence.[116] Cranberry products at these dosages are expensive (over $US1000 annually, 2008 costings) and unlikely to be covered by a prescription drug benefit plan because of their classification as either foodstuffs or nutriceuticals.

10. Conclusions

Cranberry has undergone extensive evaluation over several decades in the management of UTIs. At present, there is no evidence that cranberry can be used to treat UTIs. Hence, the focus has been on its use as a preventative strategy. Cranberry has been effective *in vitro* and *in vivo* in animals for the prevention of UTI. It appears to work by inhibiting the adhesion of P-fimbriated uropathogens (e.g. uropathogenic *E. coli*) to the uroepithelium, thus impairing colonization and subsequent infection. The isolation of the component(s) of cranberry with this activity has been a daunting task, considering the hundreds of compounds found in the fruit and its juice derivatives. Reasonable evidence suggests that the anthocyanidin/proanthocyanidin moieties are potent antiadhesion compounds. However, problems still exist with standardization of cranberry products, which makes it extremely difficult to compare products or extrapolate results. Unfortunately, most clinical trials have been fraught with design deficiencies and none have evaluated specific key cranberry-derived compounds considered likely to be active moieties (e.g. proanthocyanidins). In general, the preventive efficacy of cranberry has been variable and modest at best. Meta-analyses have established that recurrence rates over 1 year are reduced approximately 35% in young to middle-aged women. The efficacy of cranberry in other groups (i.e. elderly, paediatric patients, those with neurogenic bladder, those with chronic indwelling urinary catheters) is questionable. Ongoing clinical trials include a randomized controlled trial of cranberry versus cotrimoxazole in UTI prophylaxis in premenopausal women,[117] and a randomized, controlled, dose-ranging trial of cranberry-containing products in UTI prophylaxis in women with recurrent UTIs.[118] Withdrawal rates have been quite high (up to 55%), suggesting that these products may not be acceptable over long periods. Adverse events include gastrointestinal intolerance, weight gain (due to the excessive caloric load) and drug-cranberry interactions (due to the inhibitory effect of flavonoids on CYP-mediated drug metabolism). The findings of the Cochrane Collaboration support the potential use of cranberry products in prophylaxis of recurrent UTIs in young and middle-aged women. In light of the heterogeneity of clinical study designs and

the lack of consensus regarding the dosage regimen and formulation to use, cranberry products cannot be recommended for the prophylaxis of recurrent UTIs at this time.

Addendum in Proof

McMurdo and colleagues[119] have published the results of a 6-month randomized, double-blind trial comparing low-dose trimethoprim (100 mg at bedtime) and cranberry extract (Cran-Max, 500 mg tablet at bedtime) in the prevention of recurrent UTI in older women (at least 45 years old). Participants had experienced at least two UTIs in the previous year. A total of 137 women were randomized (69 to cranberry, 68 to trimethoprim). Thirty-nine (28%) had a recurrent symptomatic UTI (25 with cranberry, 14 with trimethoprim). The relative risk of the difference in proportions was non-significant (1.616; 95% CI 0.93, 2.79; p = 0.084). In addition, the differences in the time to first UTI recurrence and the median times to recurrence were non-significant (p = 0.1 and p = 0.479, respectively). Premature study withdrawal occurred in 9% of cranberry and 16% of trimethoprim recipients (p = 0.205). Adverse event rates were similar in the two groups. Although this is the first cranberry-versus-antimicrobial UTI prevention study, this study has not definitively established a role for cranberry at this time. Prophylaxis rates were lower than expected for both products, compromising study power. This is likely to be the reason why the trend to superiority of trimethoprim did not achieve statistical significance. In addition, no details were provided regarding the cranberry product and its standardization of content.

Acknowledgements

No funding was provided for the preparation of this article. The author has no conflict of interests that are directly relevant to the content of this review.

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