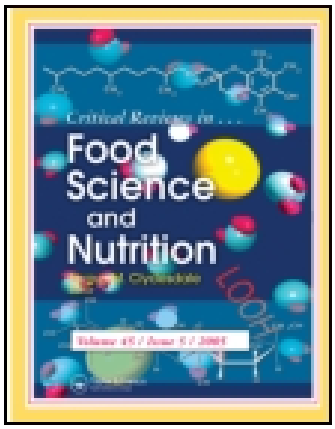

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Cranberry and Recurrent Cystitis: More than Marketing?

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Cranberry and Recurrent Cystitis: More than Marketing?

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Epidemiologic studies indicate that millions of people suffer from recurrent cystitis, a pathology requiring antibiotic prophylaxis and entailing high social costs. Cranberry is a traditional folk remedy for cystitis and, which, in the form of a variety of products and formulations has over several decades undergone extensive evaluation for the management of urinary tract infections (UTI). The aim of this retrospective study is to summarize and review the most relevant and recent preclinical and clinical studies on cranberries for the treatment of UTIs. The scientific literature selected for this review was identified by searches of Medline via PubMed. A variety of recent experimental evidence has shed light on the mechanism underlying the anti-adhesive properties of proanthrocyanidins, their structure–activity relationships, and pharmacokinetics. Analysis of clinical studies and evaluation of the cranberry efficacy/safety ratio in the prevention of UTIs strongly support the use of cranberry in the prophylaxis of recurrent UTIs in young and middle-aged women. However, evidence of its clinical use among other patients remains controversial.

Keywords Cranberry, recurrent cystitis, proanthiocyanidine, phytotherapy

INTRODUCTION

Urinary tract infections (UTI) are among the most common bacterial infections and have the heaviest impact on welfare budgets and people's quality of life. UTIs consist of clinical signs and symptoms arising from the genitourinary tract together with the presence of microorganisms in the urine exceeding a threshold value for significance (ranging from 102 to 103 colony-forming units/mL).

UTIs are classified as either lower infections (confined to the bladder; commonly called cystitis), or upper infections (present in the renal parenchyma; also called pyelonephritis), and as either uncomplicated or complicated. An uncomplicated UTI is one occurring in a normal host who has no structural or functional abnormalities, is not pregnant, or who has not been instrumented (e.g., with a catheter). All other UTIs are considered complicated (Foxman, 2010). Cystitis, seen much more frequently than pyelonephritis, is typically characterized by dysuria, frequency, and urgency, with or without suprapubic pain (Guay, 2008). Symptoms and classification of UTIs are summarized in Table 1. Single UTI episodes are very common, especially in adult women, with women showing a 50-fold higher rate of infection than adult men. Recurrent UTIs, defined as two or more episodes over six months or three or more episodes over one year (this definition applicable only to young women with acute uncomplicated UTIs), are also common, occurring in up to one-third of women after first-episode UTIs. Cystitis is generally self-limiting, but is usually treated with antibiotics that may affect both the intestinal and the vaginal microflora, causing side effects such as colitis, vaginal yeast infections, and antibiotic resistance.

Use of alternative strategies such as cranberry therapies for the prophylaxis of recurrent UTIs may be the best to prevent cystitis and preserve the effectiveness of our current antibiotics.

In this review, we present a broad overview of what lies beyond the empirical use of cranberry in UTIs, summarizing the most recent evidence supporting its clinical use.

The paper is divided into the following five sections regarding the relevance of cranberry to urinary tract infection: 1. Review criteria, 2. Pharmacognosy, 3. Pharmacology, 4. Clinical evidence for the use of cranberry in UTIs, and 5. Conclusions.

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Table 1 Common UTIs symptoms and diagnosis

Organ	Disease	Symptoms	Diagnosis
Bladder	Uncomplicated lower UTI/Cystitis	Dysuria, frequency, urgency	Urinalysis; urine culture if pyelonephritis is suspected, or if symptoms >2–4 days
Kidney	Pyelonephritis	Flank pain, nausea and vomiting, fever (>38°C), or costovertebral angle tenderness	Urinalysis; urine culture; abdomen ultrasound scan Unenhanced helical computed tomography (CT), excretory urography, or dimercaptosuccinic acid (DMSA) scanning, should be considered if the patients remain febrile after 72 h of treatment
Bladder and/or Kidney	Complicated UTI with/without pyelonephritis	Infection associated with a condition, such as a structural or functional abnormality of the genitourinary tract, or the presence of an underlying disease that interferes with host defense mechanisms, which increase the risks of acquiring infection or of failing therapy	Rule out and manage the cause of genitourinary tract abnormality

REVIEW CRITERIA

Studies selected for this review were identified by searches of Medline via PubMed and references from relevant articles. Search keywords included cranberry, phytotherapy, *Vaccinum macrocarpon*, urinary tract infection, natural drugs, cystitis, recurrent cystitis, PACs, and *Escherichia coli*.

The literature published in English over the last 15 years (from January 1994 to February 2011) was reviewed, but some earlier relevant papers were also included.

PHARMACOGNOSY

The English term "cranberry" is used to indicate the group of small evergreen shrubs constituting the *Oxycoccos* sub-genus of the *Vaccinium* genus (Ericaceae). *Vaccinium erythrocarpon* Michx., *Vaccinium macrocarpon* Aiton, *Vaccinium microcarpon* (Turcz. ex Rupr.) Schmalh, and *Vaccinium oxycoccos* L. are the four species belonging to this sub-genus. These are prostrate plants with slim branches which are not completely woody and bear small coriaceous leaves. The flowers are white with a shade of dark pink; the fruit is a berry which is larger than the flowers and initially white before ripening into a bright red.

Vaccinium macrocarpon Aiton, called "large cranberry", "North American cranberry" "bearberry", or simply "cranberry" is a member of the Ericaceae family and differs from the other species belonging to the sub-genus Oxycoccus by its larger leaves. It is native to North America and grows mainly in the northeastern United States, Wisconsin, Canada, and the Pacific Northwest (Neto et al., 2008). *Vaccinium macrocarpon* berries are edible and were included in the diet of Native Americans who employed them for the treatment of bladder and kidney ailments and as dyes (Dugoua et al., 2008). The use of *V. macrocarpon* juice to treat UTIs and wounds is reported in different manuals of phytotherapy.

V. macrocarpon berries have attracted public attention due to their potential health benefits (Neto, 2007). Recently, cranberries have been found to be rich in phenols, which exhibit potent antioxidant activity (Sun et al., 2002; Zheng and Wang, 2003), prevent bacterial adhesion to host cells in UTIs of *Escherichia coli*, and stomach ulcers (Howell et al., 1998; Burger et al., 2000; Foo et al., 2000a), as well as prevent the co-aggregation of many oral bacteria (Steinberg et al., 2005; Weiss et al., 2005). In addition, they exhibit in vitro anticancer activity (Bomser et al., 1996; Sun et al., 2002), protect against lipoprotein oxidation (Wilson et al., 1998; Chu and Liu, 2005), and reduce cholesterol in vivo (Reed et al., 2001).

Many of these bioactivities have been linked to the presence of a very wide variety of phytochemicals in cranberries. They contain >80% water and 10% carbohydrates, vitamins, mineral salts, organic acids (citric, malic, and quinic acids, small amounts of benzoic and glucuronic acids), and phenolic compounds including three classes of flavonoids [flavonols, anthocyanins, and proanthocyanidins (PACs)], catechins or flavan-3-ols and phenolic acids, among which the major is *p*-hydroxycinnamic acid. Triterpenoids of the ursane type have also been detected (Raz et al., 2004; Neto, 2007). The major anthocyanins in cranberry are galactosides and arabinosides of cyanidin and peonidin shown in Figure 1a and b (Fuleki and Francis, 1968). Anthocyanin content can range between 25 and 91 mg per 100 g of ripe berry at harvest depending on cultivar (Wang and Stretch, 2001). Quercetin is the major flavonol in cranberries and exists in several glycosidic forms (Figure 1c), primarily the 3-O-galactoside (Yan et al., 2002; Vvedenskaya and Vorsa, 2004). Myricetin glycosides are also present in lesser quantity (Figure 1d). The total flavonol content of cranberry fruit averages 20–30 mg per 100 g fresh berry weight (Neto, 2007).

Cranberry PACs are primarily dimers, trimers, and larger oligomers of epicatechin or poly-flavan-3-ols (Figure 2). They contain two types of linkages between epicatechin units: the more common $4\beta\rightarrow8$ linkage (B-type) and a less common A-type linkage featuring both $4\beta\rightarrow8$ and $2\beta\rightarrow8\rightarrow O\rightarrow7$ interflavan bonds. The combination of linkages means that cranberry PACs are very diverse in three-dimensional (3-D) structure (Neto et al., 2008). *V. macrocarpon* berry contains a significant quantity of ursolic acid in its peel, in the aglycone form and as the *cis*- and *trans p*-hydroxycinnamate esters shown in Figure 3 (Murphy et al., 2003).

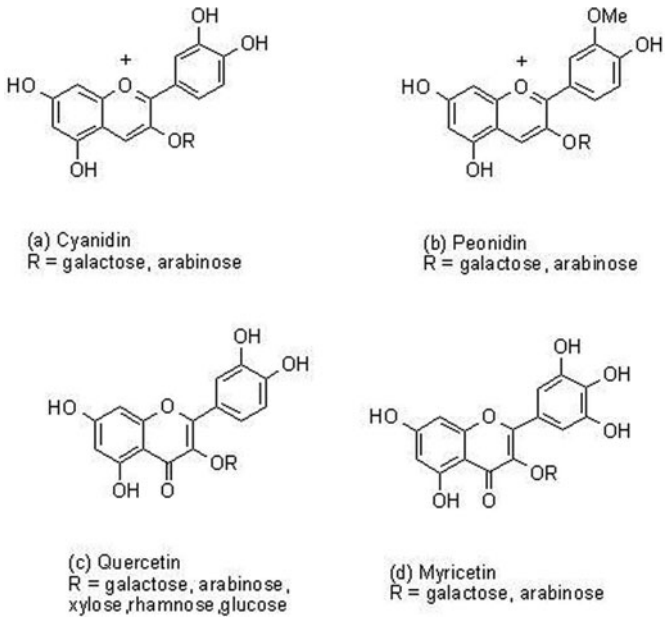

Figure 1 Cyanidin (a) and Peonidin (b) the major anthocyanin glycosides; Quercetin glycosides (c) the major flavonols in Vaccinium macrocarpon berry; Myricetin glycosides (d) also present in lesser quantities.

Today, most commercial cranberry farms are located in the northern United States, Massachusetts, New Jersey, and the Canadian provinces of Quebec and British Columbia. Commercial harvests occur in September and October. Cranberries can be processed into fresh berries, concentrate, sauce products, and juice drinks (sweetened and non-sweetened). The single-strength juice is very acidic (pH = 2.5) and unpalatable. The leading brand of cocktail contains 33% pure cranberry juice. Dried cranberry powder formulated in capsules or tablets is also available. Some products available on the market are standardized to total organic acids or polyphenolic content.

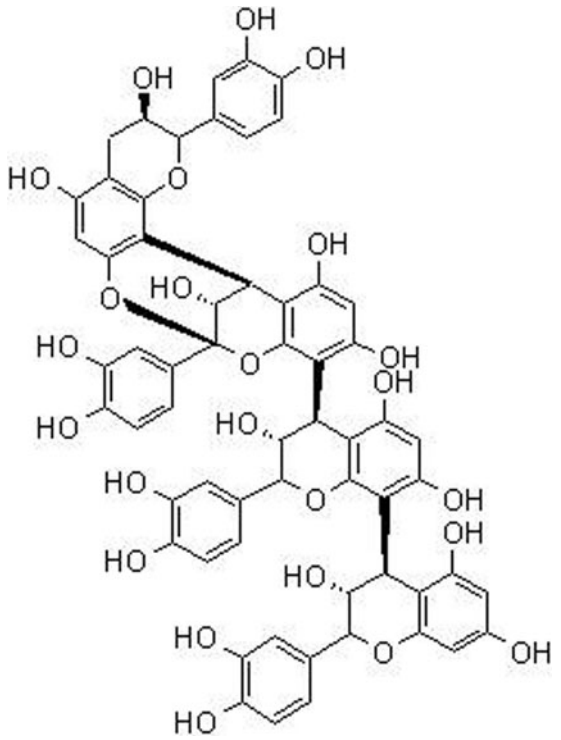

Figure 2 Structure of a typical V. macrocarpon proanthocyanidin tetramer composed of epicatechin units with one A-type linkage.

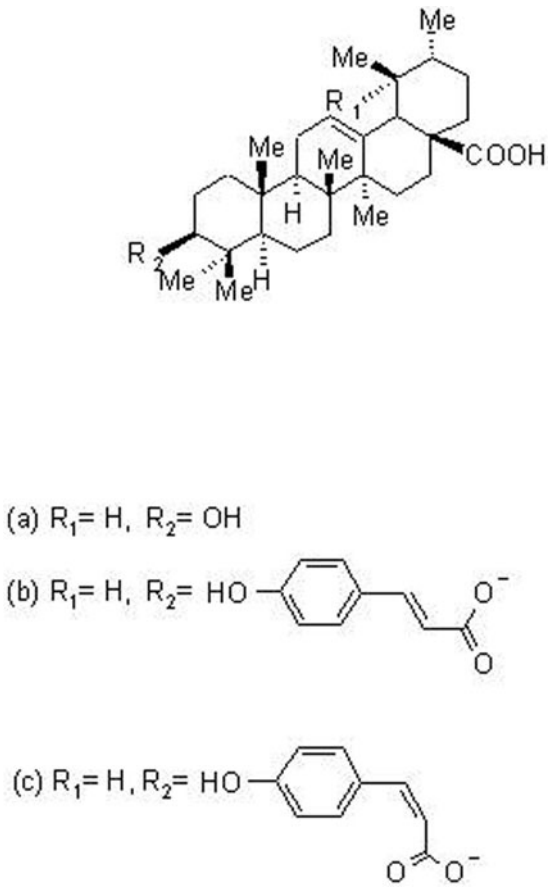

Figure 3 The triterpenoid Ursolic Acid (a) and its hydroxycinnamate esters (b) and (c) isolated from whole V. macrocarpon berry.

PHARMACOLOGY

Epidemiology of UTIs

UTIs are very common infections in otherwise healthy women (about 13 million women each year in the United States and approximately 150 million people worldwide), with an incidence that ranks second only to respiratory infections. It has been estimated that 40% of women develop at least one UTI episode during their lifetimes. In 2006, UTIs were responsible for 11 million physician visits, 1.7 million emergency room visits, and almost half a million hospitalizations (Nielubowicz and Mobley, 2010). The frequency of acute cystitis among young women is 0.5–0.7 episodes per person per year (Hooton et al., 1996). Approximately 25% of young females with acute cystitis develop recurrent UTIs within six months and, in those with a history of one or more UTIs, the risk of a second within

one year was found to be 70% (Foxman, 2010). A relevant number of women affected by UTIs (more than a third) is treated with antimicrobial therapy, with remarkable costs to healthcare systems. In 2006 the societal expenditure for these infections amounted to $3.5 billion in the United States alone (Nielubowicz and Mobley, 2010), equivalent to nearly $2.5 billion in 2010, adjusted for inflation. This amount was similar to those in other developed countries.

Although UTIs can occur in both men and women, females are about 50 times more likely to contract UTIs compared with males, especially because women have closer proximity of the urethra to the anus and a shorter urethra (three to five centimeters) that allows bacteria to ascend more easily into the bladder. Males are less vulnerable because their urethras are longer (about 18 cm) and because prostatic fluid serves as an antibacterial shield. However, in men older than 50 years, the incidence of UTIs rises dramatically (anywhere from 20 to 50% prevalence) because enlargement of the prostate (benign prostatic hypertrophy) may lead to failure to completely eliminate urine from the bladder, thus easing the growth of bacteria. In women, the incidence of infection also increases with age due to the postmenopausal loss of estrogen causing a change in the vaginal flora that, in turn, results in periurethral colonization with pathogen agents.

Several risk factors may increase the risk of UTI generation, such as bladder or uterine prolapse that may occur in older women. These factors also include high sexual intercourse frequency; the use of oral contraceptives, diaphragm, and spermicides; pregnancy; and catheters placed in the bladder of both males and females (Finer and Landau, 2004). Moreover, women with recurrent UTIs have been shown to have an increased susceptibility to vaginal colonization with uropathogens, and colonization with Gram-negative bacilli was heavier and longer-lasting compared with women without a history of recurrent UTIs. This difference between women with and without recurrent UTIs seems to result from a greater propensity for uropathogenic coliforms to adhere to the uroepithelial cells of women with recurrent infection. The underlying cause of this difference has not been determined, although, as also mentioned by Finer and Landau (2004), in some cases this may be genetically determined. Epidemiologic evidence and several case reports suggest that uropathogenic *Escherichia coli* (UPEC) is transmitted mostly through sexual activity. This hypothesis is supported by the evidence that risk of UTIs is associated with a higher frequency of vaginal intercourse and with a new sex partner. Moreover, UTIs occur especially among women in the age range 18–29 years, a time of life when most likely to be initiating sexual activity (Foxman, 2010).

Etiopathogenesis and Treatment of UTIs

Up to 85% of uncomplicated UTIs are caused by UPEC, which is a Gram-negative, facultative anerobic bacteria different from the *E. coli* strains that normally inhabit the gastrointestinal tract, UPEC being better adapted to living within the urinary tract and evading the host's immune response (Stamm, 2002). Moreover, UPEC possess specific uroepithelial cell attachment factors called fimbriae, allowing them to adhere to urinary epithelium more strongly than the same species obtained from other sources. Not all strains of *E. coli* are capable of causing UTIs. The other ten to 15% of UTIs are caused by streptococci and staphylococci species. In rare cases, *Candida albicans* can cause UTIs (e.g., in diabetic patients).

The first step of both acute and recurrent UTI generation is the colonization of the vaginal introitus with uropathogenic organisms originated in the rectal flora, followed by ascension of the bacteria up the urethra. The second step is adherence of the bacteria to the host bladder wall uroepithelial cells by fimbriae (Types 1, P, S, and Dr), proteinaceous macromolecules that strengthen the bond and disables the bacteria's elimination by the normal urine flow (Mulvey, 2002). Paradoxically, the shear stress of urine flow enhances the adherence of the UPEC (Thomas et al., 2004). P-fimbriae has a terminal receptor for the "P" antigen (or pyelonephritis-associated pili) that contains a D-galactose-D-galactose residue. This antigen is a blood group marker which binds not only to red cells, but also to a specific galactose dissaccharide that is also found on uroepithelial cells and the surface of cells lining the vagina and the perineum. Approximately 75% of the population expresses the P antigen, and these individuals are particularly susceptible to UTIs. This antigen is also found in vaginal and prostatic secretions which are protective because they bind to the bacterial receptor, preventing binding of the UPEC to the surface epithelium. Individuals most susceptible to UTIs would be those who express P antigen on their cells and lack P antigen in their secretions (Kaper et al., 2004). Fimbriae incorporate FimH, an adhesin that recognizes mannose and binds to mannosylated residues on the integral membrane proteins called uroplakins (UP), expressed by the bladder superficial epithelium, by which they mediate the attachment. FimH are important also in promoting internalization of *E. coli* and formation of intracellular bacterial communities (IBCs) which mature into biofilm-like structures inside individual cells. IBCs provide protection from host immune defenses and from antibiotics, enhancing bacterial cell survival and constituting a pathogen reservoir that may serve as a source for recurrent UTI. In this manner, UPEC may survive for several months in quiescent intracellular reservoirs (QIR) establishing a chronic infection state in the bladder which, under the right circumstances, may lead to multiple relapses (Anderson et al., 2004; Rosen et al., 2007; Nielubowicz and Mobley, 2010).

Uncomplicated symptomatic acute cystitis and/or urethritis are usually treated with antibiotics that are not always effective and can cause adverse effects (ADR) such as known antibiotic resistance and alteration of the normal vaginal microflora (Tempera et al., 2009). This combination may contribute to persistent genital microorganism colonization and the rise of UPEC resistance. Long-term, low-dose antibiotic treatment may be necessary in women with frequent UTI recurrences to prevent future infections, but it also leads to the rise of ADR incidence, increasing the risk of a subsequent infection.

Therefore, prudent use of antibiotics for treatment of uncomplicated UTI is recommended; this could include the therapeutic use of cranberry that has been advocated for the prevention and treatment of UTIs.

Mechanisms of Action of Cranberry

Cranberries were being used as a medicine by Native Americans before 1620 AD and have been used as a urinary antiseptic for more than 200 years (Gunn, 1878). At present, a large body of evidence shows that the dietary intake of berry fruits has a positive impact on human health and disease (Seeram, 2008). In 1923, Blatherwick and Long 1923 proposed that cranberry acted by producing acidic urine due to the excretion of hippauric acid formed from abundant benzoic acid. Hippauric acid is a strong bactriostatic agent that was once thought to have the potential to acidify urine, but this theory was later disproved. Indeed, at normal dosage, despite the acrid taste of the cranberry, ingestion does not alter urinary pH so much so much as inhibit bacterial growth (Bodel et al., 1959; Guay, 2009).

Urinary salicylate levels appear to increase significantly after regular ingestion of cranberry juice up to levels that may be obtained after the ingestion of low-dose aspirin (Duthie et al., 2005), but the relevance of this observation to date is unstudied. Another explanation of the usefulness of cranberry juice in UTIs was the non-enzymatic generation of nitric oxide (NO) by dismutation of nitrite to NO and NO_2 under mildly acidic conditions (MacMicking et al., 1997). NO possesses potent antimicrobial activities that, in part, may contribute to the antimicrobial effect of cranberry juice (Rhee and Charles, 2004). It has now been established that cranberry prevents bacterial adherence to uroepithelial cells, thus reducing the development of UTIs. Sobota (1984) was the first to suggest this hypothesis, showing that urine from subjects fed with a cranberry cocktail exhibited significant anti-adherence detected in human urine. In 1989, Zafriri and colleagues suggested that cranberry juice inhibited adherence of type 1 fimbriated *E. coli* because of its fructose content, a hypothesis without further scientific support.

The current consensus is that the major mechanism by which cranberry prevents UTIs involves inhibition of the binding of the P-fimbriae of UPEC via mannose-specific, lectin-like structures to mannose-like residues on mucosal cells. This assumption is supported by evidence that the interaction of *E. coli* with uroepithelial cells is mediated by a receptor containing D-mannose, as both D-mannose and methyl γ-D-mannopyranoside (αMM) inhibited this adherence in a dose-dependent manner and displaced the uropathogens from their attachment sites on epithelial cells (Ofek et al., 1977). Moreover, αMM has been shown to dose-dependently reduce UPEC colonization in mice (Aronson et al., 1979). However, the fine mechanisms by which cranberry inhibits the interaction of UPEC fimbriae with their mucosal receptors remain unclear. Recently Liu et al. (2006) suggested that cranberry juice decreases the adhesion forces of P-fimbriated *E. coli* using a model surface on which alteration of their conformation changed from an extended to a more spherical cell-like form, thus facilitating their elimination. Further study indicated that cranberry juice cocktail significantly decreases nanoscale adhesion strength between P-fimbriated *E. coli* HB101pDC1 cells and uroepithelial cell receptors, disrupting ligand–receptor bonds at the single-cell level (Liu et al., 2008, 2010). Moreover, Ahuja et al. (1998) provided *in vitro* evidence supporting cranberry juice's irreversible inhibition of P-fimbriae of *E. coli* expression, as assessed by transmission electron microscopy. Consistent with this finding, Johnson et al. (2008) also used scanning electron microscopy to reveal a decrease in the visible p-fimbriae in *E. coli* cultured in the presence of cranberry juice or PACs purified from whole cranberries. Furthermore, cranberry juice inhibited biofilm formation of P-fimbriated *E. coli* (Di Martino et al., 2005).

Numerous in vitro studies have evaluated the effects of cranberry on bacterial adhesion to model surfaces such as uroepithelial cells, showing its ability to prevent bacterial adherence to cells as well as to cause detachment of adherent bacteria from cells (see Guay, 2009). Other evidence provided in animal and in human subjects has supported this assumption (see Guay, 2009). Experiments conducted to identify the component(s) of cranberry responsible for its anti-adhesive properties have shown that the major constituent responsible are PACs, polyphenolic metabolites widely distributed in higher plants which have been ascribed several potential positive health benefits including antibacterial and chemotherapeutic activities (Seeram, 2008). The first to identify PACs as the compounds in cranberries responsible for preventing uropathogenic phenotypes of P-fimbriated *E. coli* from adhering to the urinary tract were Howell et al. in 1998. Commercially available cranberry powder and increasing PAC extract concentrations also inhibited adherence of *E. coli* to vaginal epithelial cells in a linear, dose-dependent relationship over a PAC concentration range of 75 to 5 μg/mL (Gupta et al., 2007). This vaginal effect may be relevant both for the prevention of UTIs and for the maintenance of the normal vaginal ecosystem, although clinical studies are required (Pérez-López et al., 2009). However, cranberry PACs do not inhibit adhesion of type 1 *E. coli* to uroepithelial cells. Cranberry PACs are composed of oligomers and polymers of flavans, and their specific structure may influence biological activity. They can be distinguished into two types of PACs. The B-type PACs, present in tannin-rich foods such as grapes and chocolate, in which the flavan-3-ol units (epicatechin or catechin) are often linked through a single bond. A less common structural feature of PACs is the A-type linkage, in which exists a second ether linkage between an A-ring of the lower unit and C-2 of the upper unit (O7 $\rightarrow$ C2). PACs isolated from cranberry berry consist of predominantly epicatechin units with at least one unusual double A-type linkage which may be important structural features in the anti-adhesion process (Foo et al., 2000a). Several years later after 1998, Howell et al. (2005) compared the in vitro anti-adhesion activity of A-linked PAC from cranberry juice with that of B-linked PAC from commercial grape and apple juices, green tea,

and dark chocolate, showing the lack of anti-adhesion activities of B-linked PAC as compared with the A-linked PAC, thus suggesting that the latter may be responsible for abridged bacterial adherence to uroepithelial cells, thus reducing the development of UTIs. Moreover, in vitro research (Foo et al., 2000b) showed that the PACs trimers possessing A-type interflavanoid linkages isolated from the ripe berries of cranberry are more effective in preventing adherence of P-fimbriated *E. coli* isolates from the urinary tract to cellular surfaces containing α-Gal(1$\rightarrow$4)β-Gal receptor sequences, similar to those on uroepithelial cells (epicatechin-(4$\beta\rightarrow$6)-epicatechin-(4$\beta\rightarrow$8, 2$\beta\rightarrow$O$\rightarrow$7)-epicatechin; epicatechin-(4$\beta\rightarrow$8, 2$\beta\rightarrow$O$\rightarrow$7)-epicatechin; epicatechin-(4$\beta\rightarrow$8)-epicatechin-(4$\beta\rightarrow$8, 2$\beta\rightarrow$O$\rightarrow$7)-epicatechin). On the other hand, further constituents of cranberry juice such as fructose, vitamin C, and 1-O-methylgalactose had minimal to no effect on in vitro adherence of *E. coli* to mucosal surfaces (Sobota, 1984; Turner et al., 2005).

Kinetics, Dosage, and Safety of Cranberry

It is known that oral absorption of flavonoids is more efficient with the intake of natural glycosylated forms as opposed to the aglycone (nonglycosylated) forms. The glycosylated forms compete with glucose for intestinal sodium/glucose cotransporter (SGLT1). However, only five percent of ingested flavonoids reach the circulation, the flavonol forms being able to do this most easily. Flavonoids not absorbed in the small intestine are subjected to microbial degradation in the colon. PAC polymers may undergo biotransformation into sulfate esters or glucoronide-conjugated metabolites by colonic microflora (Santos-Buelga and Scalbert, 2000), and may be degraded into phenolic acids which can be found in human urine following consumption of PAC-rich chocolate (Rios et al., 2003). Scalbert and Williamson (2000) suggested that the chemical and physical properties of PACs in the unmodified form are responsible for their poor absorption by the gut. Even if hydrolysis occurs, monomers and trimers are largely metabolized by liver first-pass extraction, thus suggesting that the concentration of dietary phenolics in plasma may be lower than necessary to achieve the same results in vivo (Scalbert and Williamson, 2000). Further, Dearing et al. (2002) proposed that any compounds in the urinary tract initially derived from PACs in cranberry juice would be vastly different than the original (unmodified) one. However, both cranberry PACs and/or metabolites could be active in the colon as well as in the urinary tract. They could bind to uropathogenic rectal *E. coli* isolates, thereby rendering them anti-adherent before possible introduction into the urinary tract, or they could alter the bacterial selection pressure in the colon to favor nonadherent strains (Howell, 2007). Peak urinary anthocyanidin concentrations are seen three to six hours after intake of cranberry; urinary excretion is nearly completed within the first 12 hours and totally recovered after 24 hours (Ohnishi et al., 2006). However, flavonoids are difficult to quantify in plasma after ingestion of cranberry products because of their tight binding to plasma proteins and red/white blood cell membranes. In contrast, it is much easier to quantify free phenolic acids in plasma after cranberry ingestion (Ruel and Couillard, 2007). Moreover, the unusual heterogeneous structures of the A-linked cranberry PACs may be biotransformed to unique biologically active urinary metabolites or even reach the urine intact as dimers or trimers (Howell, 2007).

Scientific literature is rich in studies conducted on administering cranberry in different ways and dosages. Oral delivery of ^{14}C-labeled grape PACs to rats resulted in 19% of the dose being excreted in urine, and 45% in feces (Harmand and Blanquet, 1978). In humans, a commonly recommended amount of cranberry for UTI prevention is daily consumption of 300 mL of cranberry juice containing 36 mg PACs measured using the DMAC (dimethylaminocinnamaldehyde) method, which clinically reduced bacteriuria and pyuria (Avorn et al., 1994). Very recently, an excellent study (Howell et al., 2010) has evaluated the dosage regimes and collection time-periods following ingestion of a PAC-standardized cranberry powder (18 or 36 mg) with the aim of investigating persistence in urine over a broader time period and to determine the most effective dose of PAC equivalents per day. A randomized, double-blind versus placebo multilcenter study recruited 32 volunteers from Japan, Hungary, Spain, and France with the aim of determining if the urinary anti-adhesion effect following consumption of cranberry is universal within the population or is specific to certain ethnicities, dietary regimes, locations, etc. The study was carried out using commercially available capsules of cranberry powder in which dosages were standardized to deliver 18 or 36 mg of PAC equivalents. It showed peak urinary anti-adhesion activity six hours after ingestion of the PAC powder, with a reduction in activity at 24 hours, parallel to a linear increase in urinary anti-adhesion activity with increasing dosages of PAC equivalents at both six and 24 hours. Interestingly, anti-adhesion effect was shown 24 hours after consumption of 72 mg of PAC equivalents without differences among all volunteers (regardless of country location). Howell et al. (2010) concluded that administration of PAC-standardized cranberry powder at dosages containing 72 mg of PAC per day in two split doses of 36 mg in the morning and evening may offer some protection against bacterial adhesion and virulence in the urinary tracts.

Patient compliance regarding the ingestion of cranberry products has generally been good, and no side-effects have been associated with consuming multiple servings or supplements of cranberry products. Given the strong scientific evidence supporting its safety profile, cranberry supplementation as whole berry or juice may be a valuable therapeutic choice in the treatment of UTIs during pregnancy or breastfeeding (Dugoua et al., 2008). However, in people with a tendency to develop kidney stones or in the presence of renal impairment, it would be prudent to avoid cranberry therapy or to limit cranberry juice intake up to one liter per day. Moreover, episodes of gastric discomfort caused by excessive stomach acidity have been reported after consumption of very large daily amounts of cranberry juice.

Table 2 Trials on cranberry and women

Paper	Type of the trial	Trial duration	Population	Trial design	Endpoint(S)	Conclusion
Kontiokari et al. (2001)	Open, randomized placebo-controlled	12 months	150 women*	First group received of cranberry-lingonberry juice concentrate (50 ml/day) Second group received *Lactobacillus,* 100 mL five days a week Third group served as an open control group.	Difference in timing of recurrence of urinary tract infection	Cranberry juice reduced recurrences by about a half
Jass and Reid (2009)	Randomized crossover study	1 week	12 women	3 groups: unsweetened reconstituted cranberry juice; cranberry tablets; placebo	Determine if consuming reconstituted, unsweetened cranberry juice retained its bioactive properties by reducing uropathogen adhesion without adversely affecting urinary calcium, magnesium and the vaginal microflora.	Cranberry juice retains the ability to reduce UTI by inhibiting pathogen adhesion Cranberry did not affecting urinary pH or vaginal microbiota, or the risk of calculi.
Howell et al. (2010)	Randomized double-blind Placebo controlled	24 hours	32 women	Cranberry commercially available product vs placebo	Reduction in UPEC adhesion propriety after being in contact of urine collected after cranberry assumption	Statistically significant reduction of adhesivity after ingestion of cranberry
Barbosa-Cesnik et al. (2011)	Double-blind, placebo-controlled	6 months	319 female college students	Cranberry juice vs placebo	Detect a 2-fold difference between treated and placebo groups,	Drinking cranberry juice twice per day gave no protection against the risk of recurring UTI
Stothers (2002)	Randomized placebo controlled	12 months	150 women	Placebo juice + placebo tablets vs placebo juice + cranberry tablets, vs cranberry juice + placebo tablets	>50% decrease in symptomatic UTI's per year and a >50% decrease in annual antibiotic consumption	Both cranberry juice and cranberry tablets statistically significantly decreased the number of patients experiencing at least 1 symptomatic UTI. Cost effectiveness ratios demonstrated cranberry tablets were twice as cost effective as organic juice for prevention.

*Women who had a UTI caused by *Escherichia coli* (>10^5 colony-forming units/mL in clean voided midstream urine) and were not taking antimicrobial prophylaxis.

Table 3 Trials on cranberry and children

Paper	Type of the trial	Trial duration	Population	Trial design	Endpoint(S)	Conclusion
Nishizaki et al. (2009)	Case matched, open, placebo vs cranberry	13.7 months*	31 children with vescicoureteral reflux grade < 5 age	Cranberry juice vs placebo	Cranberry juice can be substituted for antibiotic prophylaxis in the prevention of UTI in children with VUR.	There was no significant difference in the risk of having recurrent UTI between the cranberry and cefaclor groups ($P > 0.05$). No adverse effects were seen in the cranberry juice group. Loose stools developed in one patient in the cefaclor group.
Kontiokari et al. (2005)	Randomized placebo-controlled	3 months	341 healthy children mean age 4.3 years	Cranberry juice vs placebo	Evaluate the effect of cranberry juice on nasopharyngeal and colonic bacterial flora.	Cranberry juice was well accepted and led to no change in either the bacterial flora in the nasopharynx or the bacterial fatty acid composition of stools. To evaluate how well cranberry juice is accepted by children. Evaluate its effect on infectious diseases and related symptoms.
Schlager et al. (1999)	Double-blind, placebo-controlled, crossover study	6 months	15 children receiving intermittent catheterization	Cranberry vs placebo	To determine the effect of cranberry prophylaxis on rates of bacteriuria and symptomatic urinary tract infection in children with neurogenic bladder receiving intermittent catheterization..	Cranberry concentrate had no effect on bacteriuria in this population
Ferrara et al. (2009)	Randomized placebo controlled	6 months	84 female children age 3-14	Cranberry juice‡ vs Lactobacillus drink◊ vs controls⊥	To evaluate the incidence of UTI episodes between the three populations. Evaluate drawbacks from the study and possible adverse events	Daily consumption of concentrated cranberry juice can significantly prevent the recurrence of symptomatic UTIs in children.

*median between the duration of the trial between the two groups.
‡Cranberry juice 50 ml daily ($n = 28$).
◊*Lactobacillus* drink (100 ml) on 5 days a month ($n = 27$).
⊥controls ($n = 29$).

Case reports have suggested a possible interaction between warfarin and cranberry juice/products through a mechanism that could involve inhibition of the hepatic CYP2C9-mediated metabolic clearance of warfarin by components in cranberry, or by displacing warfarin from albumin sites due to the increased salicylic acid concentration from drinking high amounts of cranberry juice (Paeng et al., 2007; Roberts and Flanagan 2011). However, several recent studies (see Zikria et al., 2010) showed that cranberry juice did not alter either the pharmacokinetic (Ansell et al., 2009; Ngo et al., 2010) or the pharmacodynamics of warfarin in patients (Mellen et al., 2010). No other interactions have been reported between cranberries and other drugs (Lilja et al., 2007).

CLINICAL EVIDENCE FOR THE USE OF CRANBERRY IN UTI

Single UTI episodes are very common, especially in adult women where there is a 50-fold predominance compared with adult men. Recurrences requiring intervention are usually defined as two or more episodes over six months or three or more episodes over one year (Foster, 2008). Relapse is defined as reinfection by the same bacterial strain within two weeks after treatment. There are several prophylaxis alternatives, the choice being based on the frequency and pattern of recurrences: continuous prophylaxis, postcoital prophylaxis, and intermittent self-treatment have all been shown to be effective in the management of recurrent uncomplicated UTIs in non-menopausal women (Linsenmeyer et al., 2004; Waites et al., 2004; Griffiths et al., 2008).

All the trials published on the use of cranberry for prophylaxis of recurrent cystitis in women showed a statistically significant reduction of UTI episodes except for one trial from Barbosa-Cesnik et al. (2011) which had the most numerous population (318 female college students); the main features of the trials examined are reported in Table 2. A minimum dose of the 36 mg of PACs have been established as the minimum active dose in the trial by Howell et al. (2010); this threshold is also reported in the 2010 European Urology Association guidelines (Naber et al., 2001). To date, no direct comparison between cranberry prophylactic therapy and standard antibiotic therapy in women has been published.

Because of its properties (good tolerance, low risk of inducing bacterial resistance, and absence of cross reaction with other drugs), cranberry has also been administered in children. Recurrent UTIs prophylactic treatment may benefit children with anatomic or functional abnormality of the urinary tract as well as healthy children suffering from recurrent cystitis; mean features of the trial examined are reported in Table 3. Results of trials evaluating cranberry for the prevention of cystitis in children with some kind of urologic affection are in conflict; cranberry seems to be helpful in patients with vescicoureteheral reflux, although not for those with neurogenic bladder. However, clinical evidence for the use of cranberry in pediatric patients is limited and further studies could help to determine whether this drug plays a role in recurrent cystitis prevention in this category of patient. A trial published in 2009 by Ferrara et al. is interesting in that it showed cranberry consumption reduced UTI episodes among a population of healthy children, these data being homologous to those referring to healthy women. Elderly patients have several factors predisposing to recurrent UTIs, such as benign prostate hyperplasia, chronic urinary retention or urinary incontinence, prolapse of pelvic organs, stool impaction, and physical and cognitive decline. An alternative to standard pharmacologic therapy appears desirable in a contemporary scenario of an elderly polypharmacy population. Despite these factors theoretically supporting the use of cranberry, results of the trials are also in these cases not univocal, although direct comparison between cranberry and antibiotic shows similar outcomes between the two drugs, with less adverse events for the cranberry treatment (Table 4). Almost all persons with neurologic impairment

Table 4 Trials on cranberry and elderly

Paper	Type of trial	Trial duration	Population	Trial design	Endpoint(S)	Conclusion
Avorn et al. (1994)	Randomized placebo controlled	Six months	153 elderly women	Cranberry juice vs placebo	To determine the effect of regular intake of cranberry juice beverage on bacteriuria and pyuria in elderly women	Statistically significant reduction of pyuria and bacteriuria among the cranberry arm of the trial
McMurdo et al. (2005)	Randomised, placebo-controlled, double-blind	35 days	376 older hospitalized patients	Cranberry juice vs placebo	Reduction of UTI episodes	UTI rate was lower than anticipated, making the study underpowered and inconclusive. Significantly fewer infections with *E. coli* occurred in the cranberry juice group
McMurdo et al. (2009)	Randomized placebo vs antibiotic	Six months	137 women (age > 45 years) with at least two previous UTI	Cranberry tablets vs tripthoprim (100 mg)	Reduction of UTI episode	Trimethoprim had a very limited advantage over cranberry extract in the prevention of recurrent UTIs in older women and had more adverse effects

Table 5 Trials on cranberry and spinal cord injured (SCI) patients

Paper	Type of trial	Trial duration	Population	Trial design	Endpoint(S)	Conclusion
Linsenmeyer et al. (2004)	Double-blind placebo controlled crossover trial	Four weeks	21 patients with SCI	Cranberry tablets vs placebo	To determine the effectiveness of cranberry supplement at preventing UTIs	Positive statistically significant difference in UTI episodes in the cranberry group
Hess et al. (2008)	Randomized, double-blind, placebo-controlled trial with a crossover design	12 months	47 patients with SCI	Cranberry tablet vs placebo	To determine the effectiveness of cranberry supplement at preventing UTIs	Significant reduction of UTI was observed in the cranberry arm of the trial
Waites et al. (2004)	Randomized, double-blind, placebo-controlled study	Six months	48 patients with SCI	Cranberry juice vs placebo	To determine whether antibacterial effects of cranberry extract will reduce or eliminate bacteriuria and pyuria	Cranberry extract taken in juice form did not reduce bacteriuria and pyuria

related to spinal cord injury (SCI) have voiding dysfunction. Once the leading cause of death, urinary complications remain the leading cause of morbidity and the most common infection in persons with SCI (Eves and Rivera, 2010). Chronic urinary retention requiring urinary drainage (clean intermittent catheterization) due to neurogenic bladder brings higher frequency of multiple UTI. Results published on this topic are discordant, and it is unclear if SCI patients have a true benefit ratio (Table 5).

CONCLUSION

There is very strong evidence supporting the use of cranberry juice and derivatives in the prophylaxis of recurrent UTIs in young and middle-aged women (see Jepson and Craig, 2008). Not coincidentally, the Guideline on Urinary Tract Infections from the European Association of Urology already includes cranberry products among the alternative prophylactic methods of managing recurrent uncomplicated UTI in women (Naber et al., 2001). There is also some evidence that cranberry is effective in the elderly; however, in children or adults needing catheterization, the efficacy of cranberry is questionable. Current knowledge suggests that cranberry it is not effective in people with a neuropathic bladder. Further, there is no clear evidence that cranberry can be used to treat UTIs.

However, in judging scientific literature on the clinical use of cranberry, one must take into account several critical points. First, to our knowledge, there are a very small number of controlled trials that compare cranberry with gold standards (e.g., antibacterials) for preventing UTIs. A study started in September 2005, but not yet concluded, investigates the effect of 12 months of cranberry prophylaxis (twice-daily 500 mg capsules) in comparison with antibiotic prophylaxis (trimethoprim–sulfamethoxazole once-daily 480 mg) on the rate of recurrence of UTIs and the development of antibiotic resistance (Beerepoot et al., 2006). Theoretically, using cranberry instead of antibacterials might reduce risk for the development of antibacterial-resistant organisms, although the results supporting this have not been published. Recently, a study conducted by McMurdo et al. (2009) showed that trimethoprim (100 mg) had a very limited advantage over cranberry extract (500 mg) in the prevention of recurrent UTIs in older women and produced more adverse effects. Moreover, some reports indicate that drinking considerable amounts of cranberry juice over a long period may not be well tolerated, determining a discrete number of dropouts and lack of complete adherence to therapy. In contrast, compliance of patients for the ingestion of dried cranberry powder formulated in capsules or tablets appears to be good. Second, the variability in the cranberry products used in the clinical studies in terms of dosage and active principle content confers great difficulty in the products' comparison. Standardization of PAC content in cranberry products is hoped to allow comparative dose–response clinical studies, and determination of profile of biopharmaceutical medications, product stability, and shelf-life. Third, many of the trials suffer from various limitations, including lack of standard control and randomization, no or improper blinding, small number of patients, short trial duration, and no reported intent-to-treat analysis. Another problem limiting correct analysis of clinical data is the lack of characterization of the extracts used in some clinical studies. Insufficient description of the kind of extraction solvent (i.e., ethanol, water, chloroform), the drug/extract ratio, and titration contributes to the impossibility of establishing the most effective cranberry preparation. Addressing these issues will result in a more successful and wider use of this natural drug.

As reviewed in this paper, recent experimental evidence has shed light on the mechanism underlying the anti-adhesive properties, structure–activity relationships, and pharmacokinetics of PACs. Moreover, clinical studies have made a significant contribution in establishing the cranberry efficacy/safety ratio in the prevention of UTIs. Notwithstanding, in our opinion, further studies are needed to address the bioequivalence of different cranberry commercial formulations and to gather the other needed information reported earlier. Furthermore, biopharmaceutical research coupled with clinical studies in a multidisciplinary approach continues to merit researchers' attention and support in order to respond to the rising problem of antibiotic resistances of bacteria. This is in line with the trend toward "natural" avenues to health that confer more compliance and

acceptance of phytotherapic drugs such as cranberry compared with synthetic drugs.

ABBREVIATIONS

ADR	adverse effects
BPH	benign prostatic hypertrophy
DMAC	dimethylaminocinnamaldehyde
GLT1	S intestinal sodium/glucose cotransporter
IBCs	intracellular bacterial communities
αMM	methyl γ-D-mannopyranoside
PACs	proanthocyanidins
QIRs	quiescent intracellular reservoirs
SCI	spinal cord injury
UP	uroplakins
UPEC	uropathogenic *Escherichia coli*
UTIs	urinary tract infections

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