

# Cranberry

*Vaccinium macrocarpon* Aiton

[Fam. *Ericaceae*]

## OVERVIEW

Cranberry is a fruit native to North America, with almost 98% of the world's supply cultivated in natural and artificial bogs in the northern U.S. and Canada. Both indigenous Americans and colonists valued cranberry for its medicinal and nutritional properties. Cranberries are a high-value crop, ranking 40th in sales of all cash crops monitored by the U.S. Department of Agriculture's National Agricultural Statistical Service. Sales of cranberry dietary supplements ranked 10th in 1999 in total herb sales in U.S. food, drug, and mass-market retail outlets (increasing more than \$12 million in 1999, a 15% jump from 1998). This figure reflects sales in supplement (usually capsule) form only, and does not include supplement sales in other retail channels (natural food, multilevel, mail-order, professional). It also does not reflect sales in the mainstream market for cranberry juice, which may be increasing due to consumers' growing recognition of cranberry's health benefits for the urinary tract system.

## PRIMARY USES

- Reduction in UTI occurrence
- Kidney stones

## OTHER POTENTIAL USES

- Treatment, UTI

NOTE: Cranberry juice may reduce the need for repeated antibiotic use in the treatment of recurrent UTIs and, therefore, reduce side effects, such as vulvovaginal candidiasis. However, recurrent UTIs require proper medical diagnosis and cranberry is not a substitute for antibiotics.

## PHARMACOLOGICAL ACTIONS

Inhibits adherence of bacteria to the lining of the bladder and urethra (at normal consumption levels); urinary antiseptic (at high levels of consumption).

## DOSAGE AND ADMINISTRATION

### Internal

#### Crude preparations

NOTE: The following juice doses are based on sweetened preparations unless otherwise noted. At least 10 clinical studies conducted on sweetened cranberry juice cocktail strongly suggest the safety and efficacy of this type of preparation. Some naturopathic authors suggest that sweeteners in the juice should be avoided or minimized, and recommend patients drink plenty of fluids (at least 2 liters daily) throughout the day. Authors recommending unsweetened juice generally suggest using capsules as unsweetened juice can be unpalatable.

#### Juice

TREATMENT OF UTI: 16–32 fl. oz. daily; at least 0.5 liters (approx 18 fl. oz.) of unsweetened juice daily.

PREVENTION OF UTI: 4–32 fl. oz. daily.

RENAL STONES: 8 fl. oz., 4 times daily for several days, then 8 fl. oz., twice daily for treatment and prophylaxis of renal stones that are more soluble in an acid milieu.

#### Concentrated Juice Extract

PREVENTION AND TREATMENT OF UTI: 300–400+ mg, 2–3 times daily.

## CONTRAINDICATIONS

Potential contraindications of cranberry may be present with renal insufficiency and in persons with the potential for developing uric acid or calcium oxalate stones. However, cranberry juice containing very low amounts of oxalate was found to be safe

for individuals with calcium stones. Ingesting large quantities of cranberry juice either reduced the incidence of stone formation or reduced urinary ionized calcium associated with calcium-containing renal stones.

PREGNANCY AND LACTATION: No known restrictions during pregnancy or lactation.



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**ADVERSE EFFECTS**

None known at therapeutic dosage levels. At high dosages (more than 3–4 liters daily), diarrhea or mild gastrointestinal upset may occur.

**DRUG INTERACTIONS**

No known interactions with antibiotics or other drugs.

**CLINICAL REVIEW**

In 19 mostly uncontrolled clinical studies on cranberry including a total of 1,149 participants, all but two studies demonstrated some positive effect, primarily for urinary tract health. All of the studies investigated the effects of cranberry on the urinary tract system with the exception of one study on 13 patients with peristomal skin damage. Of three double-blind, placebo-controlled (DB, PC) studies performed on a total of 178 participants, two were conducted with statistically significant positive outcomes in

favor of cranberry prophylaxis or treatment. One used a dry cranberry extract for reducing the occurrence of UTIs in women while the other addressed treatment of bacteriuria and pyuria in elderly women. A subsequent randomized, PC, crossover study using 17 elderly patients confirmed its successful use in reducing the frequency of bacteriuria. A DB, PC study did not find cranberry juice concentrate to be effective in preventing UTIs in 15 children (ages 2–18) with neurogenic bladders, nor did another single-blind, randomized, cross-over study performed on 21 children investigating ingestion of cranberry juice cocktail vs. water for antibacterial prophylaxis in pediatric neuropathic bladders. A Cochrane review evaluated randomized, controlled trials of cranberry juice in preventing urinary tract infections and found that the trials were generally of poor quality and included a large number of dropouts. The reviewers recommended that other cranberry products, such as capsules, may prevent dropouts and that further well-designed trials are necessary.



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## OVERVIEW

Cranberry is a fruit native to North America, with almost 98% of the world supply cultivated in the northern U.S. and Canada. Both indigenous Americans and colonists valued cranberry for its medicinal and nutritional properties. Cranberries are a high-value crop, ranking 40th in sales of all cash crops monitored by the U.S. Department of Agriculture's National Agricultural Statistical Service. Sales of cranberry dietary supplements ranked 10th in 1999 in total herb sales in U.S. food, drug, and mass-market retail outlets.

## USES

Urinary tract infections (UTIs), including prevention, treatment, and decreasing occurrence; kidney stones.

## DOSAGE

### Internal

**NOTE:** The following juice doses are based on sweetened preparations unless otherwise noted. Although some authors suggest that sweeteners in the juice should be avoided or minimized, clinical studies strongly suggest that these types of products are safe and effective. Additionally, patients should drink plenty of fluids (at least 2 liters daily) throughout the day. Authors recommending unsweetened juice generally suggest using capsules as unsweetened juice can be unpleasant tasting.

### Juice

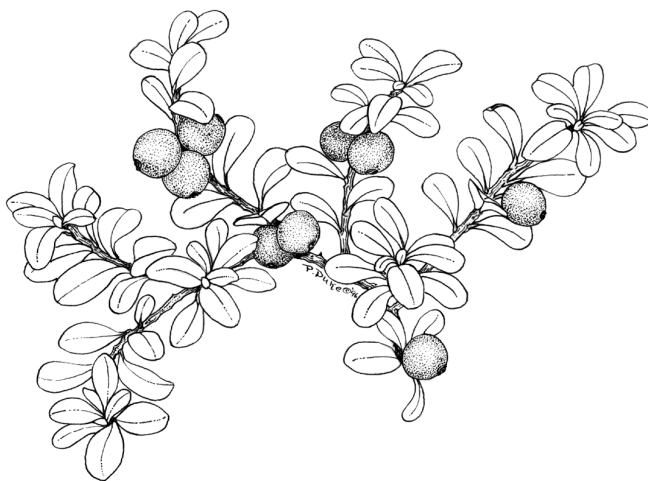
**TREATMENT OF UTI:** 16–32 fl. oz. daily or at least 17 fl. oz. of unsweetened juice daily.

**PREVENTION OF UTI:** 4–32 fl. oz. daily.

**KIDNEY STONES:** 8 fl. oz., 4 times daily for several days, then 8 fl. oz., twice daily for treatment and prevention of kidney stones that dissolve better in acid solutions.

### Concentrated Juice Extract

**PREVENTION AND TREATMENT OF UTI:** 300–400 mg, 2–3 times daily.



## CONTRAINDICATIONS

Consult a healthcare provider in cases of kidney insufficiency or tendency to develop uric acid or calcium oxalate stones.

**PREGNANCY AND LACTATION:** No known restrictions during pregnancy or lactation.

## ADVERSE EFFECTS

No adverse effects occur at recommended dosages. High dosages (more than 3–4 liters or approximately 2.5–3.5 qt. daily) may cause diarrhea or mild gastrointestinal upset.

**Caution:** If no improvement in acute infection of the urinary tract occurs within the first 24 hours of herbal treatment, seek conventional medical treatment.

## DRUG INTERACTIONS

No known interactions with antibiotics or other drugs.

## Comments

When using a dietary supplement, purchase it from a reliable source. For best results, use the same brand of product throughout the period of use. As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement with care by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions.



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# Cranberry

*Vaccinium macrocarpon* Aiton

[Fam. *Ericaceae*]

## OVERVIEW

Cranberry, a fruit native to North America, is used by the Iroquois and the Cherokee Indians as a symbol of peace and friendship (Eck, 1990). Almost 98% of the world's supply is cultivated in natural and artificial bogs in the northern United States and Canada (Vandenberg and Parent, 1999). Both indigenous Americans and colonists valued cranberry, native to Massachusetts, for its medicinal and nutritional properties.



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Indigenous Americans used cranberries in poultices for treating wounds and blood poisoning. American sailors and colonists used cranberries to prevent scurvy, similar to the use of citrus by the British. They also used cranberries and their leaves for various conditions including blood disorders, stomach ailments, liver problems, fever, “cancers,” swollen glands, and mumps. Cranberry has also been used traditionally to treat urinary tract infections (UTIs) (Avorn *et al.*, 1994). Cranberries are a high-value crop, ranking 40th in sales of all cash crops monitored by the U.S. Department of Agriculture's National Agricultural Statistical Service (USDA, 1999). Sales of cranberry dietary supplements ranked 10th in 1999 in total herb sales in food, drug, and mass-market retail outlets in the U.S., but dropped off the list of 20 leading herbs in 2001 (Blumenthal, 1999, 2001). This figure reflects sales in supplement (usually capsule) form only, and does not include supplement sales in other retail channels (natural food, multilevel, mail order, professional). It also does not reflect sales in the mainstream market for cranberry juice, which may be increasing due to consumers' growing recognition of cranberry's health benefits for the urinary tract system.

## DESCRIPTION

Cranberry preparations consist of the ripe fruit of *Vaccinium macrocarpon* Aiton [Fam. *Ericaceae*]. U.S. Pharmacopeial-grade Cranberry Liquid Preparation is a bright red juice derived from the fruits of *V. macrocarpon* or *V. oxycoccos*, containing no added

substances. Its pH is  $2.5 \pm 0.1$ , with no more than 0.05% sorbitol, or 0.05% sucrose and, not less than 2.4% dextrose, 0.7% fructose, 0.9% quinic acid, 0.9% citric acid and 0.7% malic acid. The ratio of quinic acid to malic acid is not less than 1 (USP, 2002). The Brix level (measurement of sugar content of a solution) of single strength cranberry juice is a minimum 7.5% (US FDA, 1999).

## PRIMARY USES

### Urinary tract infection (UTI)

- Reduction in UTI occurrence (Walker *et al.*, 1997; Haverkorn and Mandigers, 1994; Gibson *et al.*, 1991)

### Nephrolithiasis

- Management of kidney stones (Leaver, 1996; Light *et al.*, 1973; Sternlieb, 1963; Zinsser *et al.*, 1968)

## OTHER POTENTIAL USES

- Treatment of UTI (Leaver, 1996; Avorn *et al.*, 1994; Papas *et al.*, 1966; Sternlieb, 1963)

NOTE: Cranberry juice may reduce the need for repeated antibiotic use in the treatment of recurrent UTIs and, therefore, reduce side effects, such as vulvovaginal candidiasis. However, recurrent UTIs require proper medical diagnosis and cranberry is not a substitute for antibiotics (Brown, 2000).

## COMBINATION PREPARATIONS

Clinical and research experience has demonstrated positive results with cranberry in combination with herbs that have antibacterial activity (e.g., Chinese goldthread rhizome [*Coptis chinensis*] or goldenseal root [*Hydrastis canadensis*]) (Barney, 1996). Cranberry juice with bacteriostatic agents is recommended for long-term suppressive therapy of urinary infections in children suffering from recurrent bacterial infections. Cranberry is combined with buchu leaf (*Agathosma betulina*), three-leaved caper stem bark (*Crataeva nurvala*), and/or uva ursi leaf (*Arctostaphylos uva-ursi*) for urinary antiseptic, anti-inflammatory, astringent, antilithic, bladder tonic, and diuretic actions (Bone and Morgan, 1999). There appears to be little need for concern about interactions with uva ursi leaf because therapeutic doses of cranberry are not high enough to acidify the urine (Yarnell, 1997). Taking cranberry juice along with beneficial intestinal bacteria, such as *Lactobacillus acidophilus*, may alleviate the discomfort caused by uropathogens while restoring normal microbial balance in the gut and in vaginal mucosal surfaces (Anon, 1991).

## DOSAGE

### Internal

### Crude preparations

NOTE: The following juice doses are based on sweetened preparations unless otherwise noted. At least 10 clinical studies conducted on sweetened cranberry juice cocktail strongly suggest the safety and efficacy of this type of preparation (Jackson and

Hicks, 1997; Foda *et al.*, 1995; Avorn *et al.*, 1994; Haverkorn and Mandigers, 1994; Tsukada *et al.*, 1994; Gibson *et al.*, 1991; Kinney and Blount, 1979; Kahn *et al.*, 1967; Papas *et al.*, 1966; Bodel *et al.*, 1959). Some naturopathic authors suggest that sweeteners in the juice should be avoided or minimized, stating that consumers should not rely on sweetened cranberry juice cocktail, which contains only one-third juice mixed with water and sugar (Brown, 2000; Pizzorno and Murray, 1999; Yarnell, 1997). Capsules offer an alternative to unsweetened juice, which can be unpalatable (Brown, 2000; Yarnell, 1997). Additionally, some authors suggest patients drink plenty of fluids (at least 2 liters daily) throughout the day (Brown, 2000; Pizzorno and Murray, 1999).

### Juice

TREATMENT OF UTI: 16–32 fl. oz. daily (Leaver, 1996; Papas *et al.*, 1966; Sternlieb, 1963); at least 0.5 liters (approx 18 fl. oz.) of unsweetened juice daily (Pizzorno and Murray, 1999).

PREVENTION OF UTI: 4–32 fl. oz. daily (Leaver, 1996; Avorn *et al.*, 1994; Gibson *et al.*, 1991; Simons *et al.*, 1992; Sternlieb, 1963).

RENAL STONES: 16–32 fl. oz. daily for treatment and prevention of renal stones that are more soluble in an acid environment (Leaver, 1996; Light, 1973; Sternlieb, 1963).

### Concentrated Juice Extract

PREVENTION AND TREATMENT OF UTI: 300–400+ mg, 2–3 times daily (Brown 2000; Yarnell, 1997).

## DURATION OF ADMINISTRATION

### Internal

#### Crude Preparations

Since cranberry is a common food, there is no known limit on the duration of use. Clinical studies have lasted from 6–12 months, with one retrospective study lasting 28 months (Dignan *et al.*, 1998). The minimum time necessary to produce lowered pH for the treatment of UTI is 2–5 days (Kahn *et al.*, 1967; Fellers *et al.*, 1933), with studies showing optimal effect after 12–15 days (Rogers, 1991; Kinney and Blount, 1979; Nickey, 1975). Cranberry juice did not reduce the occurrence of bacteriuria with pyuria in elderly women until after 4–8 weeks of treatment (Avorn *et al.*, 1994).

## CHEMISTRY

Cranberry fruit contains six known anthocyanins: cyanidin-3-galactoside, cyanidin-3-glucoside, cyanidin-3-arabinose, peonidin-3-galactoside, peonidin-3-glucoside, and peonidin-3-arabinose (Hong and Wrolstad, 1986; Sapers and Hargrave, 1987); tannins, catechins, flavonol glycosides, proanthocyanidins, organic acids such as quinic, malic, and citric acids, and sugars such as dextrose and fructose (Bone and Morgan, 1999; Coppola *et al.*, 1995; Leung and Foster, 1996). Cranberries also contain proanthocyanidins with A-type, double linkages (Foo *et al.*, 2000a, 2000b). The principle characteristics of an authentic single-strength cranberry juice are reported to be: total organic acids, 2.2–3.3 g/100 g; relative percentages of organic acids, 39% quinic, 32% citric, and 27% malic; total anthocyanins by pH differential, 19.0–53.3 mg/100 g; relative percentages of anthocyanidins, 57% cyanidin, 43% peonidin; total sugars, 3.6–5.0 g/100 g; relative percentages of sugars, 79% glucose, 21% fructose (Hong and Wrolstad, 1986).

## PHARMACOLOGICAL ACTIONS

### Human

At normal consumption levels (10 fluid ounces or 300 ml per day), cranberry inhibits bacterial adherence to the lining of the bladder and urethra (Avorn *et al.*, 1994; Yarnell, 1997). At high levels of consumption (50 to 133 fluid ounces or 1,500 to 4,000 ml per day) cranberry may act as a urinary antiseptic (Blatherwick, 1914; Blatherwick and Long, 1923; Fellers *et al.*, 1933; Nickey, 1975; Kinney and Blount, 1979; Bodel *et al.*, 1959; Bone and Morgan, 1999).

### In vitro

#### Urinary tract effects

Inhibited adherence of *Escherichia coli* to uroepithelial cells (Sobota, 1984); inhibited adherence for gram-negative rods (Schmidt and Sobota, 1988); inhibited adherence of urinary *E. coli* isolates expressing type I fimbriae and type P fimbriae (Zafriri *et al.*, 1989); juice fraction selectively inhibited mannose-resistant adhesions produced by urinary isolates of *E. coli* (Ofek *et al.*, 1996); purified cranberry proanthocyanidins inhibited adherence of uropathogenic strains of P-fimbriated *E. coli* to isolated uroepithelial cells (Howell *et al.*, 1998); inhibits expression of P-fimbriae of *E. coli* (Ahuja *et al.*, 1998); inhibited adherence and colonization of some uropathogens including *E. coli* and *Enterococcus faecalis* (Habash *et al.*, 1999); oligomeric proanthocyanins and flavone-glycosides inhibited adherence of *E. coli* to human bladder cells (Walker *et al.*, 1999); cranberry proanthocyanidins with A-type linkages inhibited adherence of uropathogenic strains of P-fimbriated *E. coli* to mannose-resistant adhesion (Foo *et al.*, 2000a and 2000b).

#### Cardiovascular effects

Cranberry inhibits oxidation of human low density lipoproteins (LDL) (Wilson *et al.*, 1999); cranberry juice vasodilates rat aortae *in vitro* (Maher *et al.*, 2000); consumption of cranberry juice increases *ex vivo* antioxidant capacity (Pedersen *et al.*, 2000); oligomeric and polymeric proanthocyanidins inhibit copper-induced oxidation of human LDL (Krueger *et al.*, 2000).

#### Cancer

Proanthocyanidin fractions have potential anticarcinogenic activity (Bomser *et al.*, 1996); cranberry products inhibited proliferation of MDA-MB-435 estrogen receptor-negative and MCF-7 estrogen receptor-positive human breast cancer cells in a dose-dependent manner (Guthrie, 2000).

#### Other antiadhesion effects

Anticoaggregates subgingival microbiota (Weiss *et al.*, 1998); inhibited adherence of *Helicobacter pylori* bacteria to human gastric mucus and underlying epithelial cells (Burger *et al.*, 2000).

#### Antimicrobial

Antimicrobial against *Saccharomyces bayanus* and *Pseudomonas fluorescens* (Marwan and Nagel, 1986); a 5x concentrate of cranberry juice adjusted to pH 7 inhibited growth of certain bacteria (*E. coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*) (Lee *et al.*, 2000); inactivated polio virus type 1 (Konowalchuck and Speirs, 1978).

## MECHANISM OF ACTION

Bacterial adherence to mucosal surfaces is generally considered to be the initial event in the pathogenesis of most infectious diseases due to bacteria in humans (Beachey, 1981; Sobota, 1984). UTIs occur most frequently because of adherence of *E. coli* via P-fimbriae. The usual initiating mechanism involves bacterial adhesion



to specific molecules on cell surfaces, followed by invasive disease. The tip proteins of *E. coli* lead to the initiation of UTI (Roberts, 1996).

Cranberry's actions occur through the following mechanisms:

- Inhibits adherence of *E. coli* to the lining of the bladder and urethra (Marwan and Nagel, 1986; Ofek, 1991; Schmidt and Sobota, 1988; Sobota, 1984; Zafriri, 1989) through preventing colonization of these sites (Ofek *et al.*, 1991).
- Interrupts the binding of type 1 and P fimbriae in the gut and the bladder (Zafriri, 1989).
- A bioassay, based upon inhibition of adherence of *E. coli* to human bladder cells, human erythrocytes, and guinea pig erythrocytes, determined that the main anti-adherence components in cranberry preparations are the oligomeric proanthocyanins (OPCs) and, to a lesser extent, a secondary group of lower-molecular-weight polyphenolic substances, including flavone-glycosides (Walker *et al.*, 1999; Howell *et al.*, 1998).

Proanthocyanidins may be metabolized before reaching the bladder, suggesting that other constituents could be responsible for reducing the risk of *E. coli* infection (Reid, 1999). No studies have yet been conducted on the absorption and metabolism of cranberry proanthocyanidins, yet there is evidence of absorption of grape procyanidins (Koga *et al.*, 1999, Harmand and Blanquet, 1978).

## CONTRAINDICATIONS

Some authors have noted the potential contraindications of cranberry with renal insufficiency and in persons with the potential for developing uric acid or calcium oxalate stones (Rogers, 1991; Bone and Morgan, 1999). However, Brinkley *et al.* (1981) found that cranberry juice contained very low amounts of oxalate and was safe for individuals with calcium stones. Two small studies found that ingestion of large quantities of cranberry juice reduced incidence in stone formation or reduced urinary ionized calcium associated with calcium-containing renal stones (Zinsser *et al.*, 1968; Light *et al.*, 1973).

**PREGNANCY AND LACTATION:** No known restrictions during pregnancy or lactation (Brown, 2000; Yarnell, 1997).

## ADVERSE EFFECTS

None known at therapeutic dosage levels. At high dosage (more than 3–4 liters daily), diarrhea or mild gastrointestinal upset (Olin *et al.*, 1994; Yarnell, 1997).

## DRUG INTERACTIONS

No known interactions with antibiotics. Cranberry may enhance vitamin B12 absorption, which is useful for patients taking omeprazole, a drug used to treat ulcers (Brown, 2000).

## AMERICAN HERBAL PRODUCTS ASSOCIATION (AHPA) SAFETY RATING

Not rated (McGuffin *et al.*, 1997).

## REGULATORY STATUS

**CANADA:** Food (CFIA, 2000) or Natural Health Product (NHP) depending on label claim statement. In Canada, NHPs, also referred to as complementary medicines or traditional remedies, are subject to the Food and Drug Act and Regulations (Health Canada, 2000).

**FRANCE:** Food. No monograph in the *French Pharmacopoeia*.

**GERMANY:** Food. No German Commission E monograph (Blumenthal *et al.*, 1998). No monograph in the *German Pharmacopoeia* (DAB).

**SWEDEN:** Food. No products containing cranberry are listed in the Medical Products Agency (MPA) "Authorised Natural Remedies" (MPA, 2001).

**SWITZERLAND:** Food. No monograph in the *Swiss Pharmacopoeia*.

**U.K.:** Food. Not listed in the *General Sale List* (GSL). No monograph in the *British Pharmacopoeia*.

**U.S.:** Food (USDA, 1997) or dietary supplement depending on label claim statement (USC, 1994). Cranberry Liquid Preparation, for manufacturing purposes only, is official in the 20th edition of the *National Formulary* (NF) (USP, 2002).

## CLINICAL REVIEW

Nineteen studies, mostly uncontrolled, are outlined in the table, "Clinical Studies on Cranberry," including a total of 1,149 participants. All but two studies (Schlager *et al.*, 1999; Foda *et al.*, 1995), demonstrate some positive effect primarily for urinary tract health. All studies investigated effects on the urinary tract system with the exception of one study on 13 patients with skin damage (Tsukada *et al.*, 1994). Of three double-blind placebo-controlled (DB, PC) studies performed on a total of 178 participants (Schlager *et al.*, 1999; Avorn *et al.*, 1994; Walker *et al.*, 1997), two were conducted with statistically significant positive outcomes in favor of cranberry prophylaxis or treatment. One used a dry cranberry extract for reducing the occurrence of UTIs in women (Walker *et al.*, 1997) while the other addressed treatment of bacteriuria and pyuria in elderly women (Avorn *et al.*, 1994). A subsequent randomized, PC, crossover study on 17 elderly patients, confirmed the findings of Avorn (Haverkorn and Mandigers, 1994). The third DB, PC study did not find cranberry juice concentrate to be effective in preventing UTI in 15 children (ages 2–18) with neurogenic bladder (Schlager *et al.*, 1999), nor did another single-blind, randomized, cross-over study performed on 21 participants, investigating ingestion of cranberry juice cocktail vs. water for antibacterial prophylaxis in pediatric neuropathic bladders (Foda *et al.*, 1995). This study also did not find cranberry juice concentrate to be effective in preventing UTIs. A Cochrane Collaboration review evaluated randomized, controlled trials of cranberry juice in preventing urinary tract infections and found that the trials were generally of poor quality and included a large number of dropouts. The reviewers recommended that other cranberry products, such as capsules, may prevent dropouts and that further well-designed trials are necessary (Jepson *et al.*, 2001).

## BRANDED PRODUCTS

**Azo-Cranberry® Capsules:** PolyMedica Corporation / 11 State Street / Woburn, Massachusetts 01801 / U.S.A. / Tel: 781-933-2021 / www.polymedica.com. Capsules contain 450 mg dried cranberry extracted solids.

**Ocean Spray® Cranberry Juice Cocktail:** Ocean Spray Cranberries Inc./ One Ocean Spray Drive / Lakeville-Middleboro, MA 02349 / U.S.A. / Tel: (800) 662-3263 / www.oceanspray.com. Cocktail contains: filtered water, cranberry juice (cranberry juice and cranberry juice from concentrate), high fructose corn syrup, ascorbic acid (vitamin C).

Solaray®CranActin®: Nutraceutical Corporation / 1400 Kearns Blvd / Park City, Utah 84060 / U.S. / Tel.: (800) 669-8877 / www.nutraceutical.com. Capsules contain 400 mg dried cranberry extracted solids.

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## Clinical Studies on Cranberry (*Vaccinium macrocarpon* Aiton)

### Urinary Tract Infection

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Kontiohari et al., 2001	Urinary tract infection prevention	O, R, C n=150	12 months	50 ml of cranberry-lin-gonberry juice daily for 6 months or 100 ml of lactobacillus drink 5 days/wk for 1 year, or no intervention	Cranberry-lin-gonberry juice concentrate or lactobacillus drink	Cranberry juice, compared to lactobacillus or no intervention, significantly reduced the recurrence of urinary tract infections. The women had at least 1 recurrence at the following rates: 8 (16%) of the women in cranberry group, 19 (39%) in the lactobacillus group, and 18 (36%) in the control group. The cranberry group demonstrated a 20% reduction in absolute risk compared with the control group.
Schlager et al., 1999	Urinary tract system assessment of bacteriuria using preventive therapy	DB, PC, C n=15 children, 2–18 years, with neurogenic bladder	6 months (3-month crossover), receiving clean intermittent catheterization	60 ml/day juice concentrate (equivalent to 300 ml cranberry juice cocktail)	Specially prepared unsweetened cranberry juice concentrate (Ocean Spray®) vs. cranberry Jell-O® placebo concentrate (Kraft Foods Inc.)	Cranberry concentrate had no effect on bacteriuria, and no significant difference was observed in the acidification of urine vs. placebo. Results suggest that cranberry juice may not be effective in preventing UTIs in children with neurogenic bladder receiving intermittent catheterization.
Dignam et al., 1998	Urinary tract system	RCS, LC n=538 nursing home patients with a history of UTIs	RCS: 28 months LC: 16 months (8 months preintervention; 8 months intervention)	4 ounces juice/day or 450 mg/day	Commercial cranberry juice cocktail or Azo-Cranberry® capsules	In the cross-sectional study, symptomatic UTI rates were significantly reduced in long-term care residents. In the preintervention period of 19 months, there were 545 UTIs. For the full intervention period of 19 months, there were 164 UTIs. The Student T-test was used to compare average numbers of UTIs in preintervention with full intervention, yielding a T-value of 2.84, which is significant (p=0.0008). In the longitudinal cohort study of 113 residents for 16 months, the number of UTIs dropped from 103 in the preintervention period, to 84 during the intervention period. Although cranberry reduced the number of UTIs, the authors recommend additional well-controlled trials.
Walker et al., 1997	Urinary tract system prevention of UTIs	R, DB, PC, C n=10 women; 28–44 yrs with history of recurrent UTIs (at least 4 UTIs in the previous year or at least 1 during previous 3 months)	6 months (3 months cranberry; 3 months placebo). Treatment began after 10-day course of antibiotic therapy for symptomatic UTI. UTI treated with antibiotics was not counted in the study for enrollment criteria.	400 mg, 2x/day dry cranberry solids vs. placebo (dicalcium phosphate)	Solaray® CranActin®, each capsule contains 400 mg powdered cranberry solids	Using Student T-test and 99% confidence interval, daily consumption of cranberry extract was more effective than placebo in reducing the occurrence of UTIs (p<0.005).
Jackson and Hicks, 1997	Urinary tract system (effect on urinary pH)	PS, DCO, n=40 (21 completed study) Elderly men residing in nursing home with history of UTIs (mean age, 73 years)	3 months (4 weeks no juice, 4 weeks juice, 4 weeks no juice)	236.6 ml, 3x/day with meals	Cranberry juice (brand not stated)	Urinary pH during juice period was significantly lower than first and second non-juice periods. The findings support the claim that cranberry juice acidifies urine, even in moderate amounts. This study suggests that cranberry juice can be a home health nursing intervention to reduce risk of UTIs in the elderly.

**KEY:** C – controlled, CC – case-control, CH – cohort, CI – confidence interval, Cm – comparison, CO – crossover, CS – cross-sectional, DB – double-blind, E – epidemiological, LC – longitudinal cohort, MA – meta-analysis, MC – multi-center, n – number of patients, O – open, OB – observational, OL – open label, OR – odds ratio, P – prospective, PB – patient-blind, PC – placebo-controlled, PG – parallel group, PS – pilot study, R – randomized, RC – reference-controlled, RCS – retrospective cross-sectional, RS – retrospective, S – surveillance, SB – single-blind, SC – single-center, U – uncontrolled, UP – unpublished, VC – vehicle-controlled.

## Clinical Studies on Cranberry (*Vaccinium macrocarpon* Aiton) (cont.)

### Urinary Tract Infection (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Foda et al., 1995	Urinary tract system	R, SB, C n=21 pediatric neuropathic bladder population prophylaxes receiving clean intermittent catheterization	12 months (6 months cranberry and 6 months water)	15 ml/kg/day cocktail for 6 months; 15 ml/kg/day with water for 6 months	Cranberry juice (brand not stated)	No difference between intervention periods (2-tailed, $p=0.5566$ [whole group]; $p=0.2845$ [antimicrobial subset]) with respect to infection. 12 patients dropped out for reasons related to cranberry (taste, caloric load, cost). Fewer infections were observed in 9 patients taking juice and in 9 taking water; no difference was noted in 3 Cranberry, on a daily basis, at 15 ml/kg, did not have any effect greater than water in preventing UTI. This study does not support use of cranberry for antibacterial prophylaxis in pediatric neuropathic bladders.
Avorn et al., 1994	Urinary tract system (effect on bacteriuria and pyuria)	R, DB, PC n=153 (elderly women, mean age 78.5 years)	6 months using clean-catch urine samples	300 ml/day vs. placebo	Ocean Spray® Cranberry Juice Cocktail, vs. cranberry-flavored, vitamin C-fortified placebo	After 4 to 8 weeks of regular intake, there was a significantly reduced (95% confidence interval, $p=0.004$ ) frequency of bacteriuria and pyuria in the cranberry group. Bacteriuria with pyuria occurred in 28.1% of urine specimens of placebo group compared to 15% in the cranberry group. Cranberry reduced pre-existing bacteria in the urinary tract. Average pH of urine in the cranberry group (6.0) was higher than in the placebo group (5.5). Patients in cranberry group with bacteriuria and pyuria were more likely to convert to non-bacteriuria pyuria than in control group.
Haverkorn and Mandigers, 1994	Urinary tract system	R, PC, C n=17 (elderly patients)	8 weeks (4 weeks cranberry; 4 weeks placebo)	15 ml, 2x/day in water	Cranberry juice diluted in water (brand not stated)	This study confirmed the findings of Avorn et al. (1994), suggesting that cranberry juice reduces the frequency of bacteriuria in elderly persons. 3 patients had bacteriuria all the time and 7 at no time during the study. The remaining 7 had fewer occurrences of bacteriuria during the cranberry treatment period ( $p=0.004$ ). Increased diuresis is unlikely to be the cause of the decreased bacteriuria rate.
Gibson et al., 1991	Urinary tract system (prevention of UTI)	O n=28 (nursing home patients)	7 weeks	120–180 ml, ca./day	Cranberry Juice Cocktail, Ocean Spray®	Daily ingestion prevented UTIs in 19 of the 28 nursing home patients. The remaining 9 patients had trace or greater leukocytes and/or nitrates in all their urine and significant colony counts of Gram-negative bacilli. This study suggested that cranberry might be preventive rather than curative.
Rogers, 1991	Urinary tract system	U, MC n=16 girls with neuropathic bladders	2 weeks	180–240 ml, 2x/day for 1 week followed by 3x/day for one week	Cranberry juice (brand not stated)	All urine samples showed a reduction in both red and white cell counts, which suggests a significant reduction in infection. Urine samples from school group continued to culture <i>E. coli</i> , whereas cultures from hospital group showed a significant reduction of <i>E. coli</i> . Study suggests that cranberry juice is beneficial to children with neuropathic bladders, especially in the case of suspected infection or after bladder surgery. No statistics reported.
Schultz, 1984a	Urinary tract system (acidification of urine)	R, C n=8 (3 women, 5 men) with multiple sclerosis)	41 days (20 days cranberry treatment, 24-hour washout, 20 days orange juice)	180 ml juice, 2x/day; plus 500 mg, 2x/day ascorbic acid	Cranberry juice vs. orange juice control (brand not stated)	Cranberry juice was significantly more effective than orange juice ( $p<0.001$ ) in acidifying urine, and evening pH values were significantly lower ( $p<0.001$ ) than morning pH values (N=580).
Kinney and Blount, 1979	Urinary tract system (effect on urinary pH)	R n=40 (21 women, 19 men, mostly students) (ages 20–35 years)	12 days	4 separate groups; 150, 180, 210 or 240 ml, 3x/day with meals	Specially prepared sweetened beverage containing 80% juice, Ocean Spray®	Significant reduction in mean urine pH ( $p<0.01$ ) was observed from ingestion of cranberry juice in each of the experimental groups. Effect was not dose dependent, and there were no serious side effects.

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## Clinical Studies on Cranberry (*Vaccinium macrocarpon* Aiton) (cont.)

### Urinary Tract Infection (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Nickey, 1975	Urinary tract system (effect on urinary pH)	n=10	15 days		Cranberry juice and ascorbic acid given alone and in combination (brand not stated)	Mean urinary pH reductions from baseline during administration of cranberry juice and ascorbic acid, alone and in combination. Greatest reduction occurring with combination, with occurrence of mean urinary pH of 5.5 and 5.0 or below. No statistic reported.
Light et al., 1973	Urinary tract system	U n=15 Patients with calcium-containing renal stones (n=10). Patients without calcium-containing renal stones (n=5).	Not stated	Stone-forming patients: 32 oz. daily Normal patients: 32–80 oz. daily	Cranberry juice (brand not stated)	In patients with calcium-containing renal stones, the urinary ionized calcium was reduced with cranberry juice by an average of 50% (p<0.001). No consistent change in total or ionized calcium excretion in normals by administration of up to 480 ml juice.
Kahn et al., 1967	Urinary tract system (effect on urinary pH and calcium excretion)	U n=4 healthy, infection-free men	7–11 days	1,500–4,000 ml/day, depending on subject's liquid tolerance, 1x/day	Cranberry Juice Cocktail Ocean Spray®	3 subjects demonstrated only transient decrease in pH and increase in titratable acidity, while fourth sustained these changes for 1 week. 2 subjects experienced progressive increase in urinary calcium, despite absence of sustained urinary acidification effect. Statistics are based on each subject, not on entire group.
Papas et al., 1966	Urinary tract system (treatment of acute UTI)	U n=60 44 women and 16 men with acute UTI (All patients were symptomatic, but only 38 fit colony count criterion of 100,000 organism/ml for UTI)	21 days	ca. 450ml/day	Commercial cranberry juice product (brand not stated)	After 3 weeks of cranberry therapy, a positive clinical response was reported in 53% (32/60) of UTI patients (no urogenital complaints and fewer than 100,000 bacteria per ml urine), while an additional 20% experienced moderate improvement. During the 6 weeks after treatment period, 61% experienced recurrence. Substantial decrease in bacterial count and alleviation of urogenital complaints was significant.
Bodel et al., 1959	Urinary tract system (effects on urine pH and hippuric acid excretion)	U n=5	24 hours	1,200–4,000 ml/day	Cranberry Juice Cocktail, Ocean Spray®	Hippuric acid content of urine increased by several grams a day. Only slight changes in urine pH were reported. Bacteriostatic activity decreases five-fold when urinary pH rises to 5.6. No statistics available.
Fellers et al., 1933	Urinary tract system (effect on urine pH)	U n=6 healthy men (22–27 years)	5 days	100–300 g/day	Fresh cranberries	Cranberry ingestion increased titratable acidity, organic acids, hippuric acid, hydrogen ion concentration, and ammonia in urine, while uric acid and urea nitrogen slightly decreased. Amount of hippuric acid in urine was directly proportional to weight of cranberries eaten.

### Other

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Tsukada et al., 1994	Dermatological improvement of skin complications from urostomies	U n=13 patients with peristomal skin conditions; (average, 61.5 years)	Average 6 months (3 weeks to 2 years)	160 ml, 1–2x/day	Cranberry juice, 50% concentration (brand not stated)	An improvement in skin condition in 6 patients with erythema, maceration, or pseudoepithelia hyperplasia (PEH) and in 2 patients with maceration or PEH. Study suggests that cranberry juice improves peristomal skin PEH and maceration. Improvement was not due to acidification of urine, as the pH of the fresh urine actually became unexpectedly more alkaline (p=0.0178).

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