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.
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.
Cranberry

Vaccinium macrocarpon Aiton
[Fam. Ericaceae]

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. 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. oxyccocos, containing no added substances. Its pH is 2.5 ±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 (Cateuva nurvula), 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; Haeverkorn 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).

**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 (Zafiri 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); inhibited 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 adhesion 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 aorta *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**

Anticaggregates 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 adherence via P-fimbriae. The usual initiating mechanism involves bacterial adherence...
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; Zafirri, 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 (Zafirri, 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 proanthocyanidins (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).


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.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

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 extracts solids.

REFERENCES


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<tr>
<th>Author/Year</th>
<th>Subject</th>
<th>Design</th>
<th>Duration</th>
<th>Dosage</th>
<th>Preparation</th>
<th>Results/Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kontiokari et al., 2001</td>
<td>Urinary tract infection prevention</td>
<td>O, R, C n=150</td>
<td>12 months</td>
<td>50 ml of cranberry-lingonberry juice daily for 6 months or 100 ml of lactobacillus drink 5 days/wk for 1 year, or no intervention</td>
<td>Cranberry-lingonberry juice concentrate or lactobacillus drink</td>
<td>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.</td>
</tr>
<tr>
<td>Schlager et al., 1999</td>
<td>Urinary tract system assessment of bacteriuria using preventive therapy</td>
<td>DB, PC, C n=15 children, 2–18 years, with neurogenic bladder</td>
<td>6 months (3-month crossover), receiving clean intermittent catheterization</td>
<td>60 ml/day juice concentrate (equivalent to 300 ml cranberry juice cocktail)</td>
<td>Specially prepared unsweetened cranberry juice concentrate (Ocean Spray®) vs. cranberry Jell-O® placebo concentrate (Kraft Foods Inc.)</td>
<td>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.</td>
</tr>
<tr>
<td>Dignam et al., 1998</td>
<td>Urinary tract system</td>
<td>RCS, LC n=538 nursing home patients with a history of UTIs (at least 4 UTIs in the previous year or at least 1 during previous 3 months)</td>
<td>RCS: 28 months LC:16 months (8 months pretreatment; 8 months intervention)</td>
<td>4 ounces juice/day or 450 mg/day</td>
<td>Commercial cranberry juice cocktail or Azo-Cranberry® capsules</td>
<td>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 recommended additional well-controlled trials.</td>
</tr>
<tr>
<td>Walker et al., 1997</td>
<td>Urinary tract system prevention of UTIs</td>
<td>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)</td>
<td>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.</td>
<td>400 mg, 2x/d dry cranberry solids vs. placebo (dicalcium phosphate)</td>
<td>Solaray® CranActin®, each capsule contains 400 mg powdered cranberry solids</td>
<td>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&lt;0.005).</td>
</tr>
<tr>
<td>Jackson and Hicks, 1997</td>
<td>Urinary tract system (effect on urinary pH)</td>
<td>PS, DCO, n=40 (21 completed study) Elderly men residing in nursing home with history of UTIs (mean age, 73 years)</td>
<td>3 months (4 weeks no juice, 4 weeks juice)</td>
<td>236.6 ml, 3x/d with meals</td>
<td>Cranberry juice (brand not stated)</td>
<td>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.</td>
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### Clinical Studies on Cranberry (Vaccinium macrocarpon Aiton) (cont.)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Subject</th>
<th>Design</th>
<th>Duration</th>
<th>Dosage</th>
<th>Preparation</th>
<th>Results/Conclusion</th>
</tr>
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<tbody>
<tr>
<td>Foda et al., 1995</td>
<td>Urinary tract system</td>
<td>R, SB, C pediatric neuropathic bladder population prophylaxes receiving clean intermittent catheterization</td>
<td>12 months (6 months cranberry and 6 months water)</td>
<td>15 ml/kg/day cocktail for 6 months; 15 ml/kg/day with water for 6 months</td>
<td>Cranberry juice (brand not stated)</td>
<td>No difference between intervention periods (2-tailed, p&lt;0.0546). No subgroup analysis. 3 patients noted bacteriuria (&gt;200,000) 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.</td>
</tr>
<tr>
<td>Avorn et al., 1994</td>
<td>Urinary tract system (effect on bacteriuria and pyuria)</td>
<td>R, DB, PC n=153 (elderly women, mean age 78.5 years)</td>
<td>6 months using clean-catch urine samples</td>
<td>300 ml/day vs. placebo</td>
<td>Ocean Spray® Cranberry Juice Cocktail, vs. cranberry-flavored, vitamin C-fortified placebo</td>
<td>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 bacteriuria with pyuria than in control group.</td>
</tr>
<tr>
<td>Haverkorn and Mandigers, 1994</td>
<td>Urinary tract system (acidification of urine)</td>
<td>R, PC, C n=17 (elderly patients)</td>
<td>8 weeks (4 weeks cranberry; 4 weeks placebo)</td>
<td>15 ml, 2x/day in water</td>
<td>Cranberry juice diluted in water (brand not stated)</td>
<td>This study confirmed the findings of Avorn et al. (1994), suggesting that cranberry juice reduces the frequency of bacteriuria and pyuria by 30% 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.</td>
</tr>
<tr>
<td>Gibson et al., 1991</td>
<td>Urinary tract system (prevention of UTI)</td>
<td>O n=28 (nursing home patients)</td>
<td>7 weeks</td>
<td>120–180 ml, ca./day</td>
<td>Cranberry Juice Cocktail, Ocean Spray®</td>
<td>Daily ingestion prevented UTIs in 19 of the 28 nursing home patients. The remaining 9 patients had trace or greater leukocytes and/or nitrites in all their urine and significant colony counts of Gram-negative bacilli. This study suggested that cranberry might be preventative rather than curative.</td>
</tr>
<tr>
<td>Rogers, 1991</td>
<td>Urinary tract system (acidification of urine)</td>
<td>U, MC n=16 girls with neuropathic bladders</td>
<td>2 weeks</td>
<td>180–240 ml, 2x/day for 1 week followed by 3x/day for one week</td>
<td>Cranberry juice (brand not stated)</td>
<td>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 E. coli, whereas cultures from hospital group showed a significant reduction of E. coli. 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.</td>
</tr>
<tr>
<td>Schultz, 1984</td>
<td>Urinary tract system</td>
<td>R, C n=8 (3 women, 5 men) with multiple sclerosis</td>
<td>41 days (20 days cranberry treatment, 24-hour washout, 20 days orange juice)</td>
<td>180 ml juice, 2x/day; plus 500 mg, 2x/day ascorbic acid</td>
<td>Cranberry juice vs. orange juice control (brand not stated)</td>
<td>Cranberry juice was significantly more effective than orange juice (p&lt;0.001) in acidifying urine, and evening pH values were significantly lower (p&lt;0.001) than morning pH values (N=580).</td>
</tr>
<tr>
<td>Kinney and Blount, 1979</td>
<td>Urinary tract system (effect on urinary pH)</td>
<td>R n=40 (21 women, 19 men, mostly students) (ages 20–35 years)</td>
<td>12 days</td>
<td>4 separate groups; 150, 180, 210 or 240 ml, 3x/day with meals</td>
<td>Specially prepared sweetened beverage containing 80% juice, Ocean Spray®</td>
<td>Significant reduction in mean urine pH (p&lt;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.</td>
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</table>

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

#### Urinary Tract Infection (cont.)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Subject</th>
<th>Design</th>
<th>Duration</th>
<th>Dosage</th>
<th>Preparation</th>
<th>Results/Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nickey, 1975</td>
<td>Urinary tract system (effect on urinary pH)</td>
<td>n=10</td>
<td>15 days</td>
<td></td>
<td>Cranberry juice and ascorbic acid</td>
<td>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.</td>
</tr>
<tr>
<td>Light et al., 1973</td>
<td>Urinary tract system</td>
<td>U n=15 Patients with calcium-containing renal stones (n=10). Patients without calcium-containing renal stones (n=5).</td>
<td>Not stated</td>
<td>Stone-forming patients: 32 oz. daily Normal patients: 32–80 oz. daily</td>
<td>Cranberry juice (brand not stated)</td>
<td>In patients with calcium-containing renal stones, the urinary ionized calcium was reduced with cranberry juice by an average of 50% (p&lt;0.001). No consistent change in total or ionized calcium excretion in normals by administration of up to 480 ml juice.</td>
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<tr>
<td>Kahn et al., 1967</td>
<td>Urinary tract system (effect on urinary pH and calcium excretion)</td>
<td>U n=4 healthy, infection-free men</td>
<td>7–11 days</td>
<td>1,500–4,000 ml/day, depending on subject’s liquid tolerance, 1x/day</td>
<td>Cranberry Juice Cocktail</td>
<td>3 subjects demonstrated only transient decrease in pH and increase in titratable acidity, while fourth maintained 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.</td>
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<tr>
<td>Papas et al., 1966</td>
<td>Urinary tract system (treatment of acute UTI)</td>
<td>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)</td>
<td>21 days</td>
<td>ca. 450ml/day</td>
<td>Commercial cranberry juice product (brand not stated)</td>
<td>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.</td>
</tr>
<tr>
<td>Bodel et al., 1959</td>
<td>Urinary tract system (effects on urine pH and hippuric acid excretion)</td>
<td>U n=5</td>
<td>24 hours</td>
<td>1,200–4,000 ml/day</td>
<td>Cranberry Juice Cocktail</td>
<td>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.</td>
</tr>
<tr>
<td>Fellers et al., 1933</td>
<td>Urinary tract system (effect on urine pH)</td>
<td>U n=6 healthy men (22–27 years)</td>
<td>5 days</td>
<td>100–300 g/day</td>
<td>Fresh cranberries</td>
<td>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.</td>
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</table>

### Other

<table>
<thead>
<tr>
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<tr>
<td>Tsukada et al., 1994</td>
<td>Dermatological improvement of skin complications from stenostomies</td>
<td>U n=13 patients with peristomal skin conditions; (average, 61.5 years)</td>
<td>Average 6 months (3 weeks to 2 years)</td>
<td>160 ml, 1–2x/day</td>
<td>Cranberry juice, 50% concentration (brand not stated)</td>
<td>An improvement in skin condition in 6 patients with erythema, maceration, or pseudoepithelial 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=0.00178).</td>
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