

THE ANTIADHESION PROPERTIES OF CRANBERRY

The common folklore that advises drinking cranberry juice to stave off urinary tract infections is becoming more scientific fact. The protective effects of cranberry juice were once attributed to cranberry's high benzoic and quinic acid content, which the human body metabolizes into hippuric acid, a potent antibacterial (1). While this may be a factor in cranberry's protective results, to achieve a concentration of hippuric acid in the urine that provides this bacteriostatic effect would require the average person to drink a minimum 1500 ml (over six 8-ounce glasses) of cranberry juice per day (2,3), an unlikely amount for the average person to consume.

Recently, a number of studies have pointed to a different mechanism of action for cranberry's antibacterial effects. The American cranberry (*Vaccinium macrocarpon*) contains discrete flavonoids called condensed tannins, or proanthocyanidins (PACs), that exhibit unique microbial antiadhesion properties. Several studies have found that these PACs block uropathogenic bacteria from adhering to the uroepithelium and proliferating (4-7). New evidence also suggests this same antiadhesion activity may also be helpful in the prevention of certain ulcers and periodontal disease (8,9).

Urinary Tract Infection - Background

Urinary tract infections (UTIs) are common, painful and disruptive (10) and occur most often in women (11). Eleven percent of the female population in the United States reports having had at least one UTI a year (12). And an additional two to five percent of all women have UTI recurrences once or twice a year (13). The pathogen responsible for over 85 percent of all UTIs is *Escherichia coli* (14,15). Diagnosed UTIs are typically treated with a course of antibiotics. The incidence and virulence of UTIs has prompted a great deal of research into the role cranberry juice plays in the prevention of this uncomfortable condition.

Urine is normally sterile so in order for disease to occur, pathogenic microorganisms must first enter the urethra and adhere to host tissue. Once attached, bacteria are able to proliferate and subsequently cause clinical symptoms of infection (16). Distinct adhesins located on the cell surface of pathogens mediate attachment to complementary glyco-proteins or glycolipids on the host tissue (17). Adhesins are found on the stiff, hair-like submicroscopic structures known as fimbriae (or pili) that form bonds with a host cell receptor site. In uropathogenic bacteria, these bonds are strong enough to resist the cleansing action of urine flow (18).

Relevant Research

In 1984, Sobota (4) was among the first to investigate the potential for cranberry juice to inhibit bacterial adherence. After collecting 77 isolates of *E. coli* demonstrating adherence to uroepithelial cells obtained from women with no history of UTI, adherence inhibition was tested using three separate preparations of cranberry juice: cranberry juice cocktail (approximately 33 percent juice), cranberry concentrate and freshly prepared juice. Evidence from this *in vitro* study suggested that cranberry juice contained a factor or factors that inhibited adherence of *E. coli* to epithelial cells by interfering with a surface component of the bacteria. The cranberry juices sampled inhibited adherence at a statistically significant level up to a dilution of 1:100, with the undiluted juice demonstrating inhibition in excess of 97 percent at this concentration. This same study also

Key Points:

- Cranberry's ability to maintain urinary tract health is not due to the acids in the juice as commonly thought, but rather to distinct flavonoids in cranberries known as proanthocyanidins (PACs).
- PACs found in cranberries help prevent UTIs by blocking uropathogenic bacteria from adhering to the uroepithelium and proliferating to cause infection.
- The proanthocyanidins present in cranberries have an uncommon A-type intermolecular double linkage that appears to impart its unique antiadherence effect and is different from PACs found in other flavonoid rich foods such as grapes and chocolate.
- By preventing urinary tract infections, cranberry can help reduce the need for antibiotics, which decreases the tendency for bacteria to develop antibiotic resistance.
- New research has shown the anti-adhesion activity of cranberry's proanthocyanidin flavonoids can prevent UTIs, and possibly prevent the development of certain ulcers and periodontal disease.



established that the factor responsible for the anti-adherence properties of cranberry juice survives the normal metabolic process of humans and mice to collect in the urine. Urine samples collected from mice and humans that had ingested cranberry juice significantly impaired bacterial adherence compared to controls.

In the first randomized, double blind, placebo-controlled trial studying the effects of cranberry juice cocktail on 153 elderly women, Harvard Medical School researchers found the cranberry drink reduced the incidence of bacteriuria with pyuria in older women by almost 50 percent(19). While asymptomatic bacteriuria is common for this age group, women more than 65 years old are more likely to experience at least one UTI a year. During the six-month study period, urine analysis of study subjects consuming 300 ml (10 fluid ounces) of low-calorie cranberry juice cocktail per day showed a decrease in bacteria in the urine after the first study month compared to those drinking placebo. Subjects drinking cranberry juice also demonstrated reduced incidence of UTI during the course of the study. The researchers suggested more randomized trials with younger populations prone to UTI were necessary to further clarify the role of cranberry beverage in the prevention of this common condition (19).

Years later, a smaller, randomized crossover study in sexually active women between the ages of 18 to 45 using 800 mg of cranberry solids prepared from spray-dried cranberry juice found a statistically significant reduction in UTI recurrence for those participants taking the cranberry supplement (13). In 2001, researchers in Finland studied the UTI preventive effects of a commercially available cranberry-lingonberry juice concentrate (20). Subjects were recruited to the study after having been previously treated for a UTI caused by *E. coli*. During the six months of the study, the 50 women drinking 50 ml (1.7 fluid ounces) of the cranberry-lingonberry juice concentrate a day experienced a 20 percent absolute risk reduction in developing UTI versus the control group. More recently, Stothers (21) showed both 250 ml (8 fluid ounces) of pure unsweetened cranberry juice and concentrated cranberry tablets of similar strength reduced UTI occurrence by at least 12 percent compared to placebo.

Bioactive Factor Discovered

In an effort to determine the bioactive factor in cranberry that is responsible for its antiadherence properties, a team of researchers isolated a distinct group of compounds from cranberries. Condensed tannins, or PACs, isolated from cranberries demonstrated antiadherence activity on the P-fimbriated *E. coli* associated with UTIs at concentrations as low as 10 to 50 µg/ml (7). Moreover, further studies discovered that the PACs present in cranberries are different from those found in other foods such as grapes and chocolate. Cranberries contain a less common, high molecular weight PAC with A-type intermolecular double linkages that appear to provide its unique protective antiadherence effects (22,23).

Protection Against Antibiotic Resistant *E. coli*

Given mounting concern over the increase in antibiotic resistant *E. coli* bacteria (24), researchers are focusing more attention on alternative measures for the prevention and alleviation of UTI symptoms (25). In fact, a recent study found that urine collected from women who drank 250 ml (8.5 fluid ounces) of cranberry juice cocktail prevented the adhesion of 80 percent of 39 P-fimbriated *E. coli* isolates tested and 79 percent of the 24 antibiotic resistant strains (26). The antiadhesion activity in the subject's urine was noticeable two hours after cranberry juice consumption and lasted up to 10 hours. Of particular interest, these researchers noted that the mechanism by which cranberry juice prevents bacterial adhesion is not likely to increase selective pressure for antibiotic resistant strains.

Proposed Mechanism of Action

To date the collective data suggest two possible mechanisms of action in the preventive antiadhesion activity of cranberries: A-type PACs are metabolized relatively intact and collect in the urine to provide protective effects from bacteria that migrate from the perineum and vagina; and/or the PACs eliminated through the colon bind to uropathogenic bacteria thus decreasing the virulence of these microbes if they come in contact with the uroepithelium. Indeed, researchers have found that cranberry PACs are absorbed into the bloodstream, accounting for the former preventive effect (27). Likewise, the authors of the Finnish trial (20) stated their findings support bacterial selection in the stool because subjects in the cranberry group had no increase in UTI recurrence during the six months after they had stopped the cranberry prophylaxis.



Conclusions

Given the positive findings summarized above, the body of research exploring the benefits of cranberries on urinary tract health will likely continue to grow. The scientific evidence to date strongly supports the UTI preventive activity of this fruit. Further studies are necessary to clarify cranberry's specific role in this function.

ULCER PREVENTION – BACKGROUND

Helicobacter pylori, the spiral bacteria responsible for gastrointestinal diseases, including gastric, duodenal and peptide ulcers as well as gastric cancer (28), can be found in about half the population. Before *H. pylori* carriers show signs of infection, the bacteria must get past the protective gastric mucus layer and adhere to the underlying epithelial cells. Scientists suggest that in order to prevent infection, bacteria should be removed from this protective layer of mucosal cells, the environment most likely to harbor the bacteria in asymptomatic individuals (29).

Relevant Research

Given the antiadhesion properties cranberry has shown in studies with *E. coli*, researchers studied the effect of the high-molecular weight, non-dialysable material (NDM) from cranberries in *in vitro* adhesion studies using three strains of *H. pylori* with specificity for human gastric mucosal cells (30). Results showed NDM inhibited sialic acid-specific adhesion to human gastric mucus in a dose dependent and strain dependent manner as monitored by urease activity. As expected, significant adhesion inhibition was apparent when *H. pylori* strains were incubated with NDM (100 µg/ml), but not when mucus alone was preincubated or NDM was added after the bacteria had adhered to the mucus (30).

Recently, a more extensive study was published that tested the *in vitro* effects of NDM on the adhesion inhibition of 22 strains of *H. pylori* specific to human mucus and a human gastric cell line (31). Data show the sialic acid-specific adhesion of *H. pylori* is inhibited by NDM derived from cranberry juice. At a 0.2 mg/ml concentration of NDM, 12 strains were inhibited more than 75 percent, seven strains were partially inhibited at 35 to 74 percent, and only three were weakly inhibited. Again, detachment of *H. pylori* from mucus and epithelial cells was not observed at concentrations as high as 100 mg/ml.

Conclusions

While additional research is needed, results from these studies support the bacterial specific antiadhesion properties of NDM from cranberries. The researchers concluded that their results strongly suggest cranberry juice may inhibit the adhesion of these prevalent bacteria *in vivo*, with protective effects that may prevent the development of *H. pylori*-induced stomach ulcers (31).

PERIODONTAL DISEASE – BACKGROUND

Dental plaque harbors bacteria and other microorganisms that serve as precursors to a number of human diseases including dental caries and periodontal disease. Gram-negative anaerobic microbes that exhibit interspecies adhesion, or coaggregation behavior, appear to play a significant role in the initiation and progression of periodontal diseases (32). Coaggregation forces expressed by the bacterial colonies in dental plaque allow the bacteria to withstand the mechanical forces (such as brushing the teeth) and salivary flow that would normally displace the bacteria from the mouth (33).

Relevant Research

Research in this area has utilized a high molecular weight, non-dialysable material (NDM) extracted from cranberry juice. Given the growing evidence that supports the antiadherence activity of specific cranberry extracts, researchers performed an *in vitro* study that investigated the ability of NDM from cranberry juice to disrupt the coaggregation of bacterial species that typically inhabit the mouth and can be found in the dental plaque biofilm. Researchers found that NDM extracted from cranberry preferentially inhibited the coaggregation of 70 percent of the bacterial pairs in which at least one member was gram-negative at a concentration of 2.5 mg NDM/ml. NDM proved more effective at inhibiting coaggregation than dissociating preformed coaggregates, requiring 0.25 mg/ml and 1 mg/ml concentration respectively for the bacterial



pair tested (34). In a follow-up study exploring the effect of NDM on salivary flora, Weiss et al (33) found that saliva (1:4 dilution) and NDM (2.5mg/ml) together induce bacterial aggregation and therefore promote clearance from the oral cavity.

Conclusions

While preliminary, the evidence supporting the use of NDM isolated from cranberry in the prevention of periodontal disease is promising. The active component of NDM is known to contain PACs, the same component laboratory tests have shown to inhibit the adhesion of certain bacteria to the epithelium lining the urinary tract and possibly the stomach. Studies that elucidate the specific activity and practicality of NDM in the oral cavity are necessary in order to clarify the role of cranberry in the prevention of periodontal disease.

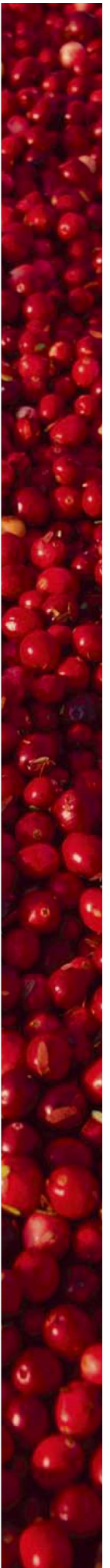
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CONCLUSIONS

Current research on the antiadhesion properties of cranberries is encouraging and compelling, with existing evidence indicating its phytonutrient components may provide beneficial protective effects in the prevention of certain bacterial diseases. However, drinking cranberry juice is in no way a substitute for the medical treatment or cure of UTIs, ulcers or periodontal disease. Further study of the PAC bioactive components of cranberries, including *in vivo* metabolism and bioavailability research, is necessary in order to determine the clinical applications for these compounds. Cranberry's role in maintaining urinary tract health is of particular interest given the increasing antibiotic resistance of UTI-specific *E.coli* strains and the need for more protective measures (26).

References:

1. Fellers, C.R., Redmon, B.C., Parrott, E.M. Effect of cranberries on urinary acidity and blood alkali reserve. *J. Nutrition.* 1933;6(5):455-463.
2. Kahn, D.H., Panariello, V.A., Sacli, J., Sampson, J.R., Schwartz, E. Implications for therapy of urinary tract infection and calculi: effect of cranberry juice on urine. *J. Am. Dietetic Assoc.* 1967;51:251.
3. Bodel, P.T., Conran, R., Kass, E.H. Cranberry juice and the antibacterial action of hippuric acid. *J.Lab. Clin Med.* 1959;54:881-888.
4. Sobota, A.E. Inhibition of bacterial adherence by cranberry juice: potential use for the treatment of urinary tract infections. *J. Urol.* 1984; 131:1013-1016.
5. Zafiri, D., Ofek, I., Pocino, A.R., Sharon, N. Inhibitory activity of cranberry juice on adherence of type 1 and type P fimbriated *Escherichia coli* to eukaryotic cells. *Antimicrob. Agents Chemother.* 1989;33(1):92-98.
6. Ofek, I., Goldhar, J., Zafiri, D., Lis, H., Adar, R., Sharon, N. Anti-*Escherichia* adhesin activity of cranberry and blueberry juices. *N. Eng. J. Med.* 1991;324(22):1599.
7. Howell, A.B., Vorsa, N., Der Mardarian, A., Foo, L.Y. Inhibition of the adherence of P-fimbriated *Escherichia coli* to uroepithelial-cell surfaces by proanthocyanidin extracts from cranberries. *N. Engl. J. Med.* 1998;339(15):1085-1086.
8. Burger, O., Ofek, I., Tabak, M., Weiss, E.I., Sharon, N., Neeman, I. A high molecular mass constituent of cranberry juice inhibit *Helicobacter pylori* adhesion to human gastric mucus. *FEMS Immunol. Med. Microbiol.* 2000;29:295-301.
9. Weiss, E.I., Lev-Dor, R., Kashmamn, Y., Goldhar, J., Sharon, N., Ofek, I. Inhibiting interspecies coaggregation of plaque bacteria with a cranberry juice constituent. *J. Am. Dent. Assoc.* 1998;129:1719-1723.
10. Ellis, A.K., Verma, S. Quality of life in women with urinary tract infections: is benign disease a misnomer? *J. Am. Board Fam. Pract.* 2000;13(6):3927.
11. Urinary Tract Infection in Adults. Available at: <http://www.niddk.nih.gov/health/urolog/pubs/utiadult/utiadult.htm>. Accessed August 29, 2002.
12. Foxman, B., Barlow, R., D'Arcy, H., Gillespie, B., Sobel, J.D. Urinary tract infection: self-reported incidence and associated costs. *Ann. Epidemiol.* 2000;10:509-515.
13. Walker, E.B., Barney, D.P., Mickelsen, J.N., Walton, R.J., Mickelsen, R.A.. Cranberry concentrate: UTI prophylaxis. *J. Fam. Prac.* 1997;45(2):167-168.
14. Leahy, M., Speroni, J., Starr, M. Latest development in cranberry health research. *Pharm. Biol.* 2002;40(Suppl.):50-54.
15. Sobel, J.D. Bacterial etiologic agents in the pathogenesis of urinary tract infection. *Med. Clin. North Am.* 1991;75:253.
16. Kuzminski, L.N. Cranberry juice and urinary tract infections: is there a beneficial relationship? *Nutr. Rev.* 1996;54(11):S87.



17. Ofek, I., Doyle, R.J. Bacterial adhesion to cells and tissues. Chapman & Hall. 1994; 578 pp.
18. Sharon, N., Ofek, I. Fighting infectious diseases with inhibitors of microbial adhesion to host tissues. *Critical Rev. Food Sci. Nutr.* 2002;42(Suppl.):267-272.
19. Avorn, J., Monane, M., Gurwitz, J.H., Glynn, R.J., Choodnovsky, I., Lipsitz, L.A. Reduction of bacteriuria and pyuria after ingestion of cranberry juice. *JAMA.* 1994;271:751-754.
20. Kontiokari, T., Sundqvist, K., Nuutinen, M., Pokka, M., Uhari, M. Randomised trial of cranberry-lingonberry juice and *Lactobacillus* GG drink for the prevention of urinary tract infections in women. *British Med. J.* 2001;322:1571-1573.
21. Stothers, L. A randomized trial to evaluate the effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. *Can. J Urol.* 2002;9(3):1558-1562.
22. Foo, L.Y., Lu, Y., Howell, A.B., Vorsa, N. The structure of cranberry proanthocyanidins which inhibit adherence of uropathogenic P-fimbriated *Escherichia coli* in vitro. *Phytochemistry.* 2000;54(2):173-181.
23. Foo, L.Y., Lu, Y., Howell, A.B., Vorsa, N. A-type proanthocyanidin trimers from cranberry that inhibit adherence to uropathogenic P-fimbriated *Escherichia coli*. *J. Nat. Prod. Chem.* 2000;63(9):1225-1228.
24. Manges, A.R., Johnson, J.R., Foxman, B., O'Bryan, T., Fullerton, K.E., Riley, L.W. Widespread distribution of urinary tract infections caused by a multi-drug resistant *Escherichia coli* clonal group. *New Engl. J. Med.* 2001;345(14):1007-1013.
25. Reid, G. The role of cranberry and probiotics in intestinal and urogenital tract health. *Crit. Rev. Food Sci. Nutr.* 2002;42(Suppl.):293-300.
26. Howell, A., Foxman, B. Cranberry juice and adhesion of antibiotic-resistant bacteria. *JAMA.* 2002;287(23):3082-3083.
27. Howell, A.B., Leahy, M., Kurowska, E., Guthrie, N. In vivo evidence that cranberry proanthocyanidins inhibit adherence of p-fimbriated *E. coli* bacteria to uroepithelial cells. *FASEB. J.* 2001;15:A284.
28. Dorrell, N., Crabtree, J.E., Wren, B.W. Host-bacterial interactions and the pathogenesis of *Helicobacter pylori* infection. *Trends Microbiol.* 1998;6:379-381.
29. Blaser, M.J. *Helicobacter pylori* eradication and its implications for the future. *Ailment. Pharmacol. Ther.* 1997;11:103-107.
30. Burger, O., Itzhak, O., Tabak, M., Weiss, E.I., Sharon, N., Neeman, I. A high molecular mass constituent of cranberry juice inhibits *Helicobacter pylori* adhesion to human gastric mucus. *Fed. Euro. Microbiol. Soc.* 2000;29:295-301.
31. Burger, O., Weiss, E., Sharon, N., Tabak, M., Neeman, I., Ofek, I. Inhibition of *Helicobacter pylori* adhesion to human gastric mucus by a high-molecular-weight constituent of cranberry juice. *Crit. Rev. Food Sci. Nutr.* 2002;42(Suppl.):279-284.
32. Moore, W.E., Moore, L.V. The bacteria of periodontal diseases. *Periodontol.* 2000. 1994;5:66-77.
33. Weiss, E.I., Lev-Dor, R., Sharon, N., Ofek, I. Inhibitory effect of high-molecular-weight constituent of cranberry on adhesion of oral bacteria. *Crit. Rev. Food Sci. Nutr.* 2002;42(Suppl.):285-292.
34. Weiss, E.I., Lev-Dor, R., Kashman, Y., Goldhar, J., Sharon, N., Ofek, I. Inhibiting interspecies coaggregation of plaque bacteria with a cranberry juice constituent. *JADA.* 1998;129:1719-1723.



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