Abstract
Urinary tract health benefits have long been ascribed to the American cranberry, *Vaccinium macrocarpon*, through folklore. Now, a growing body of science supports this association. Current research suggests that this benefit is due to components in cranberry preventing the adhesion of certain bacteria in the urinary tract. Cranberry's relatively unique A-type proanthocyanidins were identified as the components that prevented the adhesion of *P*-fimbriated *E. coli* to uroepithelial cells using bioassay-directed fractionation techniques. Very recently, using an animal model, *in vivo* evidence was obtained suggesting that cranberry proanthocyanidins were absorbed and elicited this specific anti-adherence activity in urine. Recent preliminary research suggests that cranberry's microbial anti-adhesion effect may extend into the gastrointestinal tract, which may contribute to both the urinary tract health benefit as well as preventing attachment of *H. pylori*, the bacteria responsible for many peptic ulcers. Diets high in fruits, vegetables, and grains contribute to improving health status in a number of ways. Oxidative stress may play a role in the development of many chronic diseases, including cardiovascular diseases. *Ex vivo* testing indicates that cranberry flavonoids inhibit the oxidation of human LDL cholesterol, with proanthocyanidins the most active flavonoid fraction. Additionally, a diet rich in cranberry juice powder significantly reduced the total and LDL cholesterol in hypercholesteremic pigs. Cranberry appears to be a relatively unique fruit in that it may provide benefits both through microbial anti-adhesion and possibly through antioxidant mechanisms.

Keywords: Cranberry, proanthocyanidin, anti-adhesion, *E. coli*, *H. pylori*, LDL cholesterol, antioxidant.

Cranberries and microbial anti-adhesion
The health benefits of the American cranberry, *Vaccinium macrocarpon*, have been of interest since colonial days. Cranberries, fruits native to New England, belong to the genus *Vaccinium*, which also includes *Vaccinium oxycoccus* (European cranberry or mooseberry, English mossberry, bogberry) and *Vaccinium vitis-idaea* (preiselberry, whortleberry, lingonberry) (Kuzminski, 1996). Early researchers ascribed cranberry's urinary tract benefit to its naturally high acid content. Sobota (1984) was the first to find that cranberry juice inhibited microbial adhesion. The effect most studied with regard to cranberry's anti-adhesion mechanism is the benefit to urinary tract health. New preliminary research suggests that cranberry's anti-adhesion mechanism may also provide benefits in the gastrointestinal tract and in the oral cavity.

Cranberries and urinary tract health
The term *urinary tract infection* (UTI) refers to the presence of microorganisms in the urinary tract, including the bladder, prostate, collecting system, or kidneys (National Institute of Diabetes and Digestive and Kidney Diseases, 2001). Common symptoms include frequent and urgent need to urinate, painful urination, cloudy urine, and lower back pain. *Escherichia coli* is the most common urinary pathogen, accounting for 85% of UTI's. Other pathogenic bacteria (*Enterococcus, Staphylococcus, Proteus, or Klebsiella*) can also be responsible. UTIs account for 9.6 million doctor visits annually. The cost of diagnostic work-up and treatment has been estimated at $100 per visit. The treatment of choice is an antibiotic, generally effective within three days. UTIs are one of the most common infections in females, more prevalent among women than men. It is estimated that approximately 50% of women will develop at least one UTI in their lifetime, and many will have several infections (Stanton & Dwyer, 2000). The risk and severity of UTIs dramatically increase with use of urinary catheters or ureteral stents.

For UTIs to occur, bacterial entry and proliferation must occur (Kuzminski, 1996). Proliferation requires attachment...
to urinary tract mucosal surfaces. It is believed that compounds found in cranberry act in an anti-adhesive way such that certain microbial “bugs can’t stick” and are swept away in the urine or stool. Some recent reviews examined the scientific evidence supporting cranberry’s benefit on urinary tract health (Henig & Leahy, 2000; Lowe & Fagelman, 2001; Leahy et al., 2001). The totality of clinical, epidemiological and mechanistic research supports a beneficial effect of cranberries on urinary tract health. The latest research supports a mechanism whereby cranberry’s proanthocyanidins prevent the adhesion of certain uropathogenic *E. coli* in the urinary and gastrointestinal tracts. While early research investigated a potential mechanism of urinary acidification (due to cranberries’ naturally high acidity), the evidence was equivocal (Blatherwick & Long, 1923; Nickey, 1975; Avorn et al., 1994). Those studies showing a positive effect on urinary acidification generally required consumption of large quantities of cranberry juice, much higher than that generally consumed. Increased urinary acidification does not appear to have a significant role in cranberry’s effect in maintaining urinary tract health.

Several intervention trials regarding cranberry juice and urinary tract health have been conducted. Many of the earlier trials have experimental design limitations, including lack of untreated controls, nonblinded, no use of placebo, and low number of subjects. Four recent studies provide the strongest clinical evidence supporting a beneficial effect.

Avorn et al. (1994) conducted a 6-month randomized, double-blinded, placebo-controlled trial with 153 elderly, institutionalized women. Subjects consumed 10 ounces of either a low-calorie cranberry juice cocktail (CJC) or a specially-prepared placebo drink that contained no cranberry, on a daily basis. Biomarkers assayed for urinary tract infections included bacteria in the urine (bacteriuria) and white blood cells in the urine (pyuria). They found that bacteriuria with pyuria was reduced by nearly 50% with consumption of CJC. Additionally, women in the test group with a positive urine culture in a given month had only 27% the likelihood of the control group for having their urine remain positive in the following month. This trial also investigated the effect of drinking CJC or the placebo drink on urinary acidification. They found that the mean pH was actually lower in the placebo group, indicating that urinary acidification was not the mechanism for cranberry’s beneficial effect.

Walker et al. (1997) conducted a small, 6-month randomized, double-blinded, placebo-controlled crossover trial using a cranberry dietary supplement prepared from spray-dried cranberry juice. Nineteen sexually active women, ages 18–45, participated. Subjects consumed two 400 mg capsules of cranberry solids or placebo capsules daily for three months, with opposite treatment for the next three months. The outcome measured was symptomatic UTIs with positive confirmation by urine culture. A statistically significant reduction in risk for urinary tract infections when taking the cranberry supplement was found with the ten subjects who completed the study.

Very recently, Kontiokari et al. (2001) conducted a randomized trial investigating the effect of either a cranberry-lingonberry juice beverage or a Lactobacillus GG drink (LGG) on the incidence of urinary tract infections. One-hundred-and-fifty young, sexually active women (average age of 30) with a history of at least one symptomatic UTI participated. Subjects were randomly allocated into three groups of 50, and received either 50 ml of the cranberry beverage daily for six months, or 100 ml of the LGG drink five days per week for a year, or served as open controls. The outcomes measured were first recurrence of symptomatic UTIs with positive confirmation by urine culture. At 6 and 12 months, the LGG drink showed no beneficial effect. At six months, eight (16%) of the women in the cranberry group and 18 (36%) in the control group had at least one recurrence. At 12 months, the cumulative occurrence of the first episode of recurrent UTI was still significantly different between the control and cranberry groups, even though the test group had stopped consuming the cranberry beverage group after six months. This outcome is significant in providing support for a hypothesis that consumption of the cranberry beverage in the first 6 months had changed the microbial flora in the gastrointestinal tract, acting as a prebiotic agent to reduce the uropathogenic *E. coli* colonization in the gut. Potentially, the load of uropathogenic *E. coli* in the stool would be lowered, thereby reducing the external migration of these bacteria from the GI to the urinary tract, and reducing the chance of UTI. Thus, cranberry may be acting in both the gut (the source of most uropathogens) and in the bladder in preventing colonization of certain uropathogenic bacteria.

Stothers and Stothers (2001) recently presented a study investigating the effectiveness of either cranberry juice or cranberry tablets vs. placebo as a prophylaxis against UTIs. A prospectively randomized blinded one-year trial was conducted with 150 sexually active women, ages 21–72 with a history of at least two symptomatic UTIs. Both groups consuming cranberry juice and cranberry tablets showed significant decreases in the mean number of symptomatic UTIs vs. those consuming placebo. Total antibiotic consumption was significantly decreased in the two cranberry groups as well.

The body of mechanistic research supporting beneficial effect of cranberry on urinary tract health is very compelling. Recent reviews provide details of these studies (Henig & Leahy, 2000; Lowe & Fagelman, 2001; Leahy et al., 2001). This research supports cranberry juice acting to inhibit adherence of certain bacteria to mucosal surfaces. Briefly, these studies measured the ability of various bacteria to adhere to uroepithelial cell surfaces using *in vitro* techniques and evaluated this activity in both human and animal urine after subjects drank cranberry juice. Bacteria have different types of adhesins on the fimbriae and pili that attach to epithelial cells. Cranberry juice contains a relatively unique component that inhibits certain adhesins (P-fimbriae) of some uropathogenic strains of *E. coli*. Only those juices...
from the Vaccinium genus tested (cranberry and blueberry) contained the mannose-resistant (P-fimbriated) adhesin inhibitor, whereas several other juices did not (Ozek et al., 1991). Using bioassay-directed fractionation techniques, Howell et al. (1998) identified proanthocyanidins (PACs, also known as condensed tannins) as the compounds in cranberries that are responsible for preventing P-fimbriated E. coli from adhering to the urinary tract. Vaccinium PACs are polymers of catechin and epicatechin. The higher molecular-weight trimers and oligomers had the greatest anti-adhesion activity, while monomers and dimers had little. Structural characterization using NMR indicates that cranberry and blueberry PACs have a unique A-type linkage not found in other foods (e.g. tea, grapes, wine, and cocoa) which have the more common B-linkage (Foo et al., 2000a). Three A-linked cranberry PAC trimers have been shown to prevent adhesion of P-fimbriated E. coli to bladder cells in vitro (Foo et al., 2000b). Questions remained as to bioavailability and absorption of these compounds. Very recently, a study was completed in which extracts of purified cranberry PACs were fed to mice. The urine was found to exhibit anti-adhesion activity against P-fimbriated E. coli, providing the first in vivo evidence that cranberry PACs and/or metabolites can be absorbed into the blood, and into urine, thereby eliciting this anti-adhesion effect (Howell et al., 2001). This is also significant in suggesting bioavailability for other potential health benefits.

The body of clinical and mechanistic research strongly suggests a beneficial role of cranberry juice in helping to maintain urinary tract health. Regular consumption of cranberry juice appears to reduce the risk of urinary tract infections and may be helpful in moving individuals out of an infected state. Further well-designed clinical trials are desired to build the base of evidence in various populations. Dose/response and temporal effect studies are needed. While cranberry juice may be helpful in maintaining urinary tract health, infections may pose a serious issue, and individuals experiencing UTIs should seek help from a medical professional. If untreated, serious complications may result.

Anti-adhesion: other potential body benefits

Preliminary research suggests that cranberries’ adhesion inhibitors appear to act against a number of types of bacteria, potentially providing additional health benefits. The newest research suggests that cranberries may also play another potential role in maintaining gastrointestinal health. A recent in vitro study investigated cranberry’s potential in inhibiting the adhesion of some strains of H. pylori to human mucosal cells (Burger et al., 2000). A cranberry fraction was found to inhibit adhesion of three strains of H. pylori that is mediated by a sialic acid-specific adhesin. Research is ongoing to determine cranberry’s activity against many other strains. Helicobacter pylori infections have been implicated as a major cause of gastric, duodenal, and peptic ulcers.

Cranberry’s anti-adhesion activity may also potentially play a role in maintaining oral cavity health. A recent in vitro study found that a cranberry fraction inhibits some oral bacteria from adhering to teeth. Adhesion of Streptococci and Actinomyces to the pellicle of salivary glycoproteins on tooth surfaces appears to be the first step in the formation of dental plaque, an early step in periodontal and gum diseases (Weiss et al., 1998). The stability of the plaque containing growing bacteria is a result of bacterial adhesion to the acquired pellicle, and interspecies adhesion known as coaggregation. A cranberry fraction reversed association of 49 of 84 coaggregating bacterial pairs tested in vitro, with greatest anti-adherence activity found with those pairs containing at least one Gram-negative anaerobe tested. The cranberry fraction was more effective in inhibiting coaggregation than dissociating preformed coaggregates. This research suggests that cranberry components have the potential for altering the subgingival microflora ecology, and aid in maintaining oral cavity health. Additional research is under way in a human trial to investigate cranberry’s potential for oral health benefits in specially formulated products.

While the implications of cranberry products for oral health and protection against H. pylori infection are promising, studies conducted to date have been in vitro only. More research is needed to draw better conclusions regarding cranberry’s potential role for human health in these areas.

Cranberry’s potential antioxidant benefits

Oxidative stress is believed to play a role in normal aging and in development of many chronic diseases, including cardiovascular disease, diabetes, cancer, cataracts, Parkinson’s disease, and arthritis. All fruits, including cranberries, contain a variety of phytochemicals that may contribute to inhibit oxidative reactions. Plant phenolics, including flavonoids, have demonstrated antioxidant effects in vitro or ex vivo. Diets rich in fruits and vegetables help maintain health in a number of ways, which may or may not be related to antioxidant mechanisms.

Cranberries and related fruits contain many flavonoids and phenolic acids with antioxidant or other physiologically beneficial activities. Cranberry flavonoids include anthocyanins (responsible for their red pigment), flavonols, flavan-3-ols, and proanthocyanidins. Recently, cranberries were identified as having among the highest amount of phenolic compounds of 20 common fruits tested on a fresh weight basis (Vinson, 2001). Phenolic compounds exhibit antioxidant effects in vitro. The biological significance of many of these components is unclear, since many questions remain as to their absorption, biotransformation, and ability to reach various sites in the body. While there is some evidence that anthocyanins and proanthocyanidins are absorbed, much work remains to understand distribution to various tissues and resulting activity.

With cardiovascular disease, the leading killer in the U.S. for both men and women, a key area of research is the effect
of various foods on cardiovascular health. The role of oxidative stress on cardiovascular health is actively under investigation. Many researchers believe that prevention of low-density lipoprotein (LDL) oxidation may protect against plaque formation in blood vessels. Wilson et al. (1998) found that cranberry juice inhibited chemical oxidation of human LDL cholesterol ex vivo. Reed et al. (2001a) investigated the effect of various cranberry flavonoid fractions on copper-induced oxidation of human LDL ex vivo. Of the various fractions tested, the proanthocyanidins had the greatest inhibitory effect on oxidation. However, questions remain as to the fate of these components in vivo. The recent study by Howell et al. (2001) provides evidence that cranberry PACs are absorbed, suggesting availability for this antioxidant effect in the body. Still, questions regarding further biotransformation remain, e.g., methylation, glucuronidation, or sulfonation, and these could impact solubility and antioxidant activity.

Total cholesterol and LDL cholesterol are well-accepted biomarkers in predicting cardiovascular health. In a recent preliminary study, cranberry juice powder was found to significantly decrease LDL cholesterol in familial hypercholesteremic (FH) swine (Reed et al., 2001b). Eight sows (four normal and four genetically predisposed to high cholesterol) were fed a baseline diet for 14 days, then fed either a diet supplemented with cranberry juice powder or a control diet for one month. At baseline sampling, the FH sows had about seven-times the level of total and about 11 times more LDL cholesterol than the normal swine. Feeding the cranberry juice powder significantly reduced total and LDL cholesterol in the FH swine after one week, with no effect found in the normal sows. After four weeks of feeding, the FH sows in the cranberry group showed a 22% decrease in LDL cholesterol compared to baseline. The mechanism of the reduction has not yet been determined. These preliminary studies suggest that cranberries, like other fruits, may play a role in maintaining heart health.

**Summary of conclusions from the latest studies**

A growing body of research suggests that cranberry is a relatively unique fruit in that it may provide two different pathways for health: through microbial anti-adhesion and broader benefits that may be related to antioxidant activities.

- The totality of evidence supports cranberry’s role in maintaining UTH. The evidence is consistent in supporting an anti-adhesion mechanism of certain bacteria to uroepithelial cells.
- It had previously been suggested that cranberry’s anti-adhesive agents may act in the bladder, in the gut (the source of most uropathogens), or both, by preventing colonization of these sites. The Kontiokari et al. (2001) study supports a prebiotic effect of cranberry juice in the GI tract, the source of uropathogens. Further research is warranted to determine if cranberry’s primary beneficial effect on urinary tract health is a result of activity in the bladder or in the gut.
- New preliminary research suggests that cranberry’s anti-adhesion property may extend to other benefits. In vitro research indicates that certain cranberry components may inhibit the adhesion of some strains of H. pylori to human gastric mucosal cells, as well as inhibit the coaggregation of certain oral cavity bacteria that contribute to plaque formation.
- Cranberry proanthocyanidins are relatively unique in that they have demonstrated anti-adhesion and antioxidant activity. The anti-adhesion activity appears to be related to their relatively unique A-type oligomeric linkage (most foods contain predominantly B-type linked PACs). A recent animal study has provided the first in vivo evidence that cranberry PACs are absorbed and inhibit certain pathogenic E. coli from adhering to uroepithelial cells.
- Absorption of cranberry proanthocyanidins signals their availability for antioxidant activity in the blood. This is significant in that, of the fractions of cranberry flavonoids tested, the PACs had the greatest inhibitory activity on copper-induced ex vivo oxidation of human LDL.
- A diet rich in cranberry juice powder was found to significantly reduce both total and LDL cholesterol in a pilot study with hypercholesteremic pigs. The mechanism of the reduction is unknown. Further research is warranted.
- The unique anti-adhesion activity of A-type proanthocyanidins suggests that caution must be taken in ascribing benefits to whole classes of compounds, since bioactivities may be highly variable, depending on subtle structural differences.

While cranberry’s role in maintaining urinary tract health has long been suggested by folklore, science now supports this benefit, and preliminary research suggests additional anti-adhesion and potentially antioxidant benefits. More studies are warranted to assess the role of the cranberry and other fruits in promoting our health.

**References**


