

Cranberry and Human Health Research Review

Introduction

Cranberries have a long history of use by Native Americans--not only as food, but also as a treasured medicine to treat and ward off a variety of conditions, including infections. The pilgrims were introduced to the berry by Native Americans, and we've had the pleasure of enjoying them ever since. The cranberry is one of only three commercially grown fruits native to North America, which is one reason why there are many cranberry products available for consumers. Cranberry sauce, dried fruit and juice not only taste great; they may also provide important health benefits.

Research over the past several decades has helped to explain how the little berry provides such big health payoffs. Studies have helped identify several bioactive compounds that do, in fact, provide health benefits from the mouth to urinary tract as well as the vascular system.

Cranberry Nutrition & Human Health Research

More than 200 original research and review articles have been published in peer-reviewed medical and nutrition journals about cranberries. Studies consist of analytical, animal, laboratory and human clinical trials.

A topline of the current body of research reveals:

- Cranberries are thought to provide health benefits due to their flavonoid and phytonutrient content.^{1,2} These naturally occurring compounds have antioxidant and antimicrobial benefits that are evident in the oral cavity, gastrointestinal (GI) tract and urinary tract.¹
- A specific type of flavonoid, proanthocyanidins (PAC), in cranberries provide urinary tract benefits by interfering with the ability of pathogenic P-fimbriated *Escherichia coli* (*E. coli*) to cause infections in the urinary tract..^{1,3-10}
- The majority of studies have focused on the cranberry's role in urinary tract health, but the benefits extend beyond the urinary tract. Other key areas include the berry's antimicrobial activities, cardiovascular and Type 2 diabetes, and anti-cancer properties.
- Cranberries provide numerous cardiovascular benefits. They have been shown to reduce low-density lipoprotein (LDL)-oxidation, maintain or improve high-density lipoprotein (HDL) levels, reducing platelet aggregation and improve vascular function.^{11,12}

This review provides highlights of key cranberry health research.

Cranberry, Urinary Tract Health and Antibacterial Properties

Chemical analyses of the berries show that they contain a variety of phytochemicals, including proanthocyanidins, that may provide health benefits.¹³ The primary area of research with cranberry has been on its potential to reduce incidence of recurring urinary tract infections and improving urinary tract health.¹⁴



Nearly one-quarter of all published cranberry research studies are on urinary tract infections (UTI) and antibacterial benefits. More than 70 studies including laboratory, animal, human clinical trials and review articles, have been published in peer-reviewed medical journals examining the role of cranberry juice and other cranberry extracts or supplements in maintaining a healthy urinary tract.

Cranberry has been effective in numerous laboratory studies as well as animal models to aid in the prevention of UTI.^{3,4,15-18} Many of the human clinical studies and reviews were on populations experiencing recurring urinary tract infections, such as spinal cord patients, those with chronic pelvic pain, pregnant women, women susceptible to recurrent infections, and men with known prostate health conditions.¹⁹⁻²²

Cranberry was originally thought to improve urinary tract health by lowering the pH of the urinary tract, however, more recent research shows that the uniquely structured proanthocyanidins (PAC) present in cranberry inhibit the adherence of pathogenic P-fimbriated *Escherichia coli* (*E. coli*) and they do so in a dose-dependent manner.^{1,3,5-10} Studies show that these antiadhesion benefits impact both antibiotic-susceptible and antibiotic-resistant uropathogenic *E. coli*.¹ It is now widely thought that cranberry PACs prevent bacteria from adhering to the uroepithelium of the bladder, thereby blocking the ability of *E. coli* to infect the urinary mucosa.²³⁻²⁵

Several forms of cranberry, including 27% cranberry juice cocktail as well as dried fruit and extracts of cranberry, appear to possess these unique anti-adhesion benefits that play a role in helping to maintain urinary tract health.^{10,23,26,27} A meta-analysis completed on all the human clinical trials concluded that cranberry products significantly reduced UTIs at 12 months in women that experienced recurring UTIs.²⁵ While more human, clinical trials are needed to expand on the current literature, there appears to be no downside to recommending cranberry products as part of a prudent diet especially for those with a history of recurrent UTIs.²⁴

The anti-adhesion benefits of the cranberry may extend into other tissues of the body to help prevent infections. Recently, several studies have evaluated cranberry-containing oral products to help protect against dental caries and other oral bacteria, including those responsible for periodontal gum disease, the leading cause of tooth loss as we age.^{28,29} Preliminary data show that PACs help reduce the number of bacteria in the oral cavity, but more research is needed to confirm the benefits of cranberry in inhibiting oral and gingival bacteria.^{28,29}

Lastly, preliminary trials suggest that these unique cranberry PACs also interfere with the adhesion of *Helicobacter pylori*, a leading cause of stomach ulcers, which in turn are a major cause of stomach cancer.^{30,31}

Antioxidant Capacity

Antioxidants help neutralize free radicals, which scientists believe can damage the body's DNA or genes, interfere with normal lipid metabolism and promote inflammation, thereby increasing the risk for certain cancers and chronic diseases.³²⁻³⁵ Cranberries contain naturally occurring compounds that have strong antioxidant properties. Among these compounds are the flavonoids. The cranberry flavonoids belong to three groups: anthocyanins, flavonols and proanthocyanidins.¹² Cranberries are also a particularly rich source of phenolic phytochemicals, including phenolic acids (benzoic, hydroxycinnamic, and ellagic acids) and flavonoids (anthocyanins, flavonols, and flavan-3-ols).^{11,24,32,33} Studies using various measures of antioxidant activity have revealed that cranberries and cranberry products have among the highest antioxidant capacity of fruits and fruit juices.^{2,33-37}



Cardiovascular Health

A growing body of evidence suggests that cranberry flavonoids and polyphenols may contribute to reducing the risk of cardiovascular disease (CVD) by inhibiting LDL-oxidation, maintaining or improving high-density lipoprotein (HDL) levels, reducing platelet aggregation, improving vascular function and reduction of blood pressure, among other potential cardiovascular benefits.^{11,12}

Numerous *in vitro* and *in vivo* experiments with cranberry flavonoids demonstrate that they act as potent dietary antioxidants and inhibit LDL-oxidation, inhibit platelet aggregation and adhesion, inhibit enzymes involved in lipid and lipoprotein metabolism that affect the immune response to oxidized LDL and their uptake by endothelial macrophages, may induce endothelium-dependent vasorelaxation, and may increase reverse cholesterol transport and decrease total and LDL-cholesterol.^{12,33,37,38}

Cranberry interventions have been shown to improve risk factors for cardiovascular disease among high-risk populations, including those with Type 2 diabetes.³⁹ In one study, low calorie cranberry juice cocktail has also been shown to raise HDL-cholesterol levels among abdominally obese men.⁴⁰ In the study, 250 ml of cranberry juice cocktail consumed daily showed positive increases in HDL-cholesterol concentrations. However, there was no statistically significant change at either 125 ml or 500 ml per day.⁴⁰

Published results show that short-term cranberry juice supplementation is associated with a significant increase in plasma antioxidant capacity and reduction in circulating oxidized LDL concentrations.⁴¹

Glycemic Response

Since cranberries are nutrient-rich and contain naturally occurring flavonoids, anthocyanins and PACs, it is thought that drinking cranberry juice cocktail and other cranberry beverages may not have the same glycemic response compared to a placebo beverage with the same sugar content. Current research conducted with humans suggests that the polyphenols in cranberries do, in fact, blunt the blood sugar response in humans.⁴²⁻⁴⁴ This is shown with conventional 27% cranberry juice cocktail beverages as well as reduced sugar or “light” cranberry juice cocktail products. While more research is needed, these preliminary studies suggest that cranberry juice cocktail may be an acceptable product for individuals with impaired glucose tolerance or those at risk for metabolic syndrome.

Anti-Cancer Activity

Although most of the studies have been done with cell cultures and animal studies thus far, a promising area of research with cranberry is in the chemopreventive properties of the fruit. *In vitro* studies show that cranberry reduced tumor cell growth for various types of cancer including, breast, colon, prostate and lung.^{12,32,45} PACs and other cranberry constituents are thought to contribute to the observed anticancer properties. The synergistic effects of the myriad phytonutrients are thought to inhibit oxidative DNA damage that is linked to cancer promotion and inhibit cell proliferation.^{12,34,45}

Human clinical trials with cranberry are limited to prostate cancer. Results of a study of men with elevated PSA levels treated with daily cranberry supplements for six months showed the subjects' Prostate Symptom Score improved and they had lower total prostate-specific antigen (PSA) levels.²²



Drug-Nutrient Interactions

A small number of individual case reports in the United Kingdom, and a smaller number in the United States, suggest that cranberries might interact with warfarin (Coumadin®). However, well-controlled, clinical pharmacokinetic and pharmacodynamic studies published in scientific literature do not show a clinically relevant interaction between cranberry juice and either warfarin metabolism or International Normalized Ratio (INR) in subjects on warfarin.⁴⁶⁻⁴⁸ Only one clinical trial, authored by Abdul et al, showed a modest increase in INR in 12 healthy volunteers who were not already taking warfarin.⁴⁹ In this study, a single large dose of warfarin (25 mg) and cranberry extract capsules, containing 3000 mg of cranberry juice concentrate, was used in a non-blinded, open-labeled study.

In 2006, the Journal of the American Dietetic Association published an article titled “Cranberry Does Not Affect Prothrombin Time in Male Subjects on warfarin” and found no significant interaction between the daily consumption of 250 mL of cranberry juice and warfarin.⁴⁸ Most recently, in 2009, a randomized, double-blind trial by Ansell et al published in the Journal of Clinical Pharmacology, showed no clinically relevant interaction between cranberry juice and warfarin and suggested that “other factors were likely responsible for the findings in the anecdotal case reports.”⁴⁶

Based on the current body of research, there is no clinical or mechanistic evidence suggesting that normal daily consumption of cranberry products (e.g., two 8-ounce glasses of juice per day) poses a risk of interacting with warfarin. Ultimately, it is the discretion of the physician and guidance of a registered dietitian to discuss dietary changes while on warfarin treatment.

More than 200 research and review articles have been published about cranberry and its nutritional and health benefits. These studies include analytical, laboratory, and animal and human clinical trials and are available at the Cranberry Institute website, under the Cranberry Health Research Library at: cranberryinstitute.org.

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