Cranberry and Human Health Research Review

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Introduction

The cranberry is one of only three commonly cultivated fruits native to North America. Enjoyed as cranberry sauce, dried fruit, and juice, cranberries are part of a healthful eating pattern. Research over the past several decades has helped to explain how the little red berry contributes to good health.

Cranberry Nutrition & Human Health Research

Many original research and review articles about cranberries have been published in peer-reviewed medical and nutrition journals. These include in vitro, animal, and human clinical and epidemiological studies. While the focus of this article will be on human evidence, in vitro and animal studies will be included as background information and context for research needs.

The current evidence for the relationship between cranberry and health reveals the following key points:

The majority of human studies have focused on cranberry's effect on urinary tract health. In addition, research has explored the impact of cranberries on cardiovascular disease, cancer prevention, oral health, glycemic response, and infections such as by Helicobacter pylori (H. pylori) bacteria, a cause of gastritis and peptic ulcer disease.

Studies have explored the role of the polyphenols found in cranberries. While most of the evidence is in vitro or in animals, there is evidence in human studies of cranberries and infection, inflammation, and oxidation. These studies will be reviewed in detail.

Scientists have looked at a specific type of polyphenol in cranberries, called the proanthocyanidins (PACs). Investigations have evaluated the role of PACs in the adhesion of bacteria to cells, such as those that cause infections in the urinary tract and the gastrointestinal system (including the mouth and stomach).

More research is needed to determine the optimal form, amount, and frequency of cranberry consumption that will help to reduce health risks and promote good health.

Urinary Tract Health

Urinary tract infections (UTI), defined as the simultaneous presence of genitourinary tract signs and symptoms with bacteria exceeding a significant threshold, are one of the most commonly acquired bacterial infections both in and outside of the hospital setting (Foxman and Brown 2003; Foxman 2003). Forty to 50% of women will have at least one UTI during their lifetimes, and 20 to 30% of those women will experience a recurrence (Foxman 2003). Other groups with an increased risk of UTI include infants, pregnant women, the elderly, and people with spinal cord injuries, catheters, diabetes, multiple sclerosis, compromised immune function, or urologic abnormalities.

Cranberries, particularly in the form of cranberry juice, have been widely investigated for their use in maintaining a healthy urinary tract. In order to assess the effect of cranberry compounds on the adherence of bacteria, particularly *Escherichia coli (E. coli*) to uroepithelial cells that line the wall of the bladder, scientists employ *in vitro* (studying cells outside of the body) or *ex vivo* (testing tissues, such as urine, outside of the body) methodology (Schmidt and Sobora 1988; Zafriri et al 1989). *In vitro* assessments are performed by isolating organisms outside of the human body to identify the effect of individual components and explore the basic biological function of an organism. *In vitro* studies are important for the progression of science but limited in that researchers cannot make conclusions about the impact within the human body without follow up investigations. *In vitro* and *ex vivo* are very preliminary ways to explore possible effects.

Three double-blind, randomized, placebo-controlled, crossover studies evaluated the antibacterial activity in human urine collected from participants after consuming cranberry products or supplements. First, in a trial of eight women, 12 hours after consuming 108 mg of cranberry in capsule form, urine was collected to evaluate the ability of bacteria to adhere to the human uroepithelial cells. There was a significant decrease in bacterial adherence to human uroepithelial cells after consuming the cranberry capsule compared with placebo (Lavigne et al 2008). Second, the urine of 32 women was analyzed *ex vivo* after consuming 0, 18, 36, or 72 mg PAC equivalents/day in cranberry powder capsules. There was a significant dose-dependent reduction in the bacterial adherence to human epithelial cells 24 hours after ingestion compared to placebo (Howell et al 2010).

Finally, 20 men and women consumed, in random order with a 6-day washout period between each, four 750-mL drinks composed of 250 mL placebo + 500 mL water, 750 mL placebo, 250 mL cranberry juice + 500 mL water, and 750 mL cranberry juice (Di Martino et al 2006). There were no differences in urine pH or specific gravity, but there was a dose-dependent decrease in *in vitro* bacterial adherence associated with cranberry versus placebo.

Randomized, controlled trials of cranberry's effects on UTI have been conducted in numerous groups, including children and adults, men and women with recurrent UTI, as well as those in long-term care, receiving pelvic radiological treatment for cancer, or with spinal cord injury. Many of these have been reviewed in the peer-reviewed scientific literature (Blumberg et al 2013; Opperman 2013; Jepson et al 2012; Dessi et al 2011), while this article will focus on those in women and children with recurrent UTI.

For women with recurrent UTIs, dietary approaches have been investigated because in addition to reducing risk, a non-drug solution could help improve quality of life, lower treatment costs and reduce the need for antibiotics. In a study of 150 women with recurrent UTI, there were fewer who experienced a UTI recurrence over a 12-month treatment period among those who consumed 750 mL pure cranberry juice (18%) or the same amount of cranberry concentrated in tablet form (20%) versus placebo (32%) (Stothers 2002). The total incidence or UTI was also lower with juice (30%) or tablets (39%) versus placebo (72%). Adherence was assessed by pill counts and self-reported fluid intakes.

A 125-mL serving of cranberry juice (which contained 40 mg PAC) or placebo was consumed by 213 women with recurrent UTI over 24 weeks (Takahashi et al 2013). There were no differences in UTI recurrence between these groups. However, in a subgroup of 118 Japanese women older than 50 years with acute uncomplicated cystitis, there was a lower incidence of UTI with cranberry juice versus placebo.

The two trials that reported no difference in UTI recurrence administered cranberry juice as a treatment protocol. During a 6-month treatment period, 176 women were randomized to consume 120 or 240 mL of 27% low-calorie cranberry juice daily, or placebo juice (120 or 240 mL of the placebo designed by the National Institutes of Health National Center for Complementary and Alternative Medicine) (Stapleton et al 2012). Since there were no differences between cranberry and placebo, the 120- and 240-mL groups were combined for each group for statistical analyses.

The cumulative rate of UTI was 0.29 in the cranberry group compared to 0.37 in the placebo. This study had limitations; the desired sample size was not met and thus the study was not adequately powered to show a significant effect of cranberry on the cumulative rate of UTI. Also, adherence to juice consumption was based on self-report rather than measurement of an active urinary metabolite. Because of the limitations, more research is required before a conclusion can be drawn.

In a double-blind, placebo-controlled trial among 319 college women, participants were randomly assigned to drink either 240 mL of 27% low-calorie cranberry juice cocktail twice daily or 240 mL of placebo juice twice daily for 6 months (Barbosa-Cesnik et al 2011). The recurrence rate was similar between study groups, with the active cranberry group presenting a slightly higher recurrence rate (19.3% vs 14.6%). The 14.6% recurrence among controls was much lower than the 30% rate that was anticipated based on published observational evidence. Therefore, the study may not have been powered sufficiently to detect differences. Other concerns noted by the authors include a potentially defective placebo or increased consumption of fluids in both groups.

There are additional human studies reporting positive results for cranberry consumption on the prevention of UTI in women which have some limitations. One hundred and fifty women were divided into three groups. Among those randomized to consume 50 mL of cranberry-lingonberry juice for 6 months, compared to a no-intervention control (there was no placebo), there was a 20% reduction in UTIs after 12 months (Kontiokari et al 2001). A 90-day study revealed that among subjects receiving either 500 mg (n = 21) or 1000 mg cranberry capsules (providing 14.5 mg PAC per g) daily (n = 23), there were fewer *E. coli* infections and UTI symptoms compared to those in the untreated control group (n = 16) (Sengupta et al 2011). Lastly, researchers randomly sampled 288 women in college with no history of UTIs and found that after controlling for sexual activity, regular cranberry juice consumption was associated with a lower risk of UTIs, while those that drank soft drinks had a higher odds ratio (Foxman et al 1995).

There are published studies assessing cranberry's effects in other groups at risk for UTI, which have been reviewed recently (Blumberg et al 2013). Included are three randomized controlled trials in children with recurrent UTI.

One study in girls (n=84), 3 to 14 years, administered 50 mL/day cranberry (7.5 g) lignonberry (1.7 g) concentrate juice versus 100 mL *Lactobacillus GG* for 5 days/month or no treatment over 6 months, and found a significantly lower UTI rate of 18.5% versus 42.3% and 48.1%, respectively ($p < 0.05$) (Ferrara et al 2009). In another study, 263 children were treated for 6 months with 5 mL/kg/day cranberry juice vs placebo, and monitored for a total of 12 months (Salo et al 2012). Although there were fewer recurrent UTI in children receiving cranberry versus placebo, the differences were not significant ($P = 0.21$). The UTI incidence per person year at risk was significantly lower in the cranberry group ($P = 0.03$), as were the number of days on antibiotics ($P < 0.001$). Notably, compliance was significantly lower in the cranberry group, as well ($P = 0.001$). In a third smaller study, 39 girls and 1 boy (aged 5 to 18 years) were randomized to receive 2 cc/kg 37% PAC versus no-PAC cranberry juice. Over one year, excluding the 6 patients in each group who dropped out, the average incidence of UTI was 0.4 per patient per year in the cranberry group, compared to 1.15 per patient per year in the placebo group ($p = 0.045$) (Afshar et al 2012).

Research in children with neuropathic bladders report inconsistent results. There was no effect on UTI recurrence in children who consumed 15 mL/kg/day cranberry juice cocktail compared to those who drank water over six months (Foda et al 1995). However, the 48% dropout rate may have limited statistical power. Similarly, no effect on the reduction of bacteriuria or UTI was observed in children who consumed 300 mL cranberry concentrate for three months compared to placebo (Schlager et al 1999). In a randomized, placebo-controlled, crossover trial in 20 children with neurogenic bladder caused by myelomeningocele, the median UTI rate was lower during the 6-month cranberry extract period compared to the 6-month placebo period (Mutlu and Ekinci 2012).

These studies illustrate the challenge of synthesizing results from human studies with cranberry products. Differences in study population, duration, and design, as well as cranberry product (juice, extract, powder, or pill) and placebo, have the potential to affect study outcomes. Given the outcomes noted thus far, there is a need to further clarify the form, amount, and frequency of cranberry consumption that will be beneficial, as well as who will benefit.

Oral and Gastrointestinal Health

Cranberry has been evaluated in maintaining oral health. Two reviews on oral health report that *in vitro* studies have been conducted to assess whether cranberry components inhibit adhesion of oral bacteria to tooth surfaces and epithelial cells, as well as to each other (Shmuely et al 2012; Feghali et al 2012). There is one randomized, double-blind, placebo-controlled human study assessing the effects of cranberry on oral health. Healthy volunteers who used a daily mouthwash supplemented with non-dialyzable material from cranberry, compared to those who used a placebo mouthwash, for six weeks demonstrated a significant reduction in total bacterial count, but no clinical changes in plaque or gingival indices (Weiss et al 2004).

Helicobacter pylori is a gram negative bacterium associated with gastrointestinal diseases such as gastric, duodenal, and peptic ulcers, as well as gastric cancer and lymphoma. *In vitro* research has evaluated the effect of cranberry on the adhesion of *H. pylori* to human mucus, erythrocytes, and gastric epithelial cells (Shmuely et al 2012).

Three randomized, placebo-controlled, double-blind studies investigated the role of cranberry and *H. pylori* infection. A trial in China, where *H. pylori* infection is endemic, showed that daily consumption of two 250-mL boxes of cranberry juice for 90 days was effective in yielding negative *H. pylori* test results for 14.4% of the intervention group (113 subjects) compared to 5.4% of the control group (112 subjects) among adults with *H. pylori* infection (Zhang et al 2005).

In patients infected with *H. pylori,* 170 were treated with antibiotics for one week with either 250 mL of cranberry juice or placebo twice daily, followed by daily juice or placebo for two more weeks. A control group of 712 patients were treated with antibiotics alone for one week (Shmuely et al 2007). The eradication rate for females was significantly higher in the cranberry-antibiotic group (95%) compared to both the placebo (80%) and antibiotic groups (83%).

In Chile, 295 children (6 to 16 years) who tested positive for *H. pylori* received either cranberry juice (200 mL) with lactobacillus (80 mL), placebo juice with lactobacillus, cranberry juice with placebo lactobacillus (heat-killed), or placebo juice/lactobacillus (control) (Gotteland et al 2008). The treatment lasted 3 weeks. The *H. pylori* eradication rate was significantly lower in the control group (1.5%) compared with the lactobacillus (14.9%), cranberry (16.9%), and cranberry plus lactobacillus (22.9%) groups. There was no difference between treatment groups; therefore, while either cranberry or lactobacillus may be beneficial in reducing *H. pylori* infection risk, they do not seem to work synergistically.

Cardiovascular Health

Several review articles have summarized evidence for cranberries and dyslipidemia, inflammation, oxidative stress, endothelial dysfunction, arterial stiffness, platelet function, and possibly hypertension and diabetes (Blumberg et al 2013; Neto 2007; Basu et al 2010; McKay and Blumberg 2007; Ruel and Couillard 2007; Reed 2002). Randomized controlled studies have been conducted to examine the effects of cranberry on cardiovascular risk markers such as blood lipids, blood pressure, glucose and oxidized low-density lipoprotein cholesterol (ox-LDL-C), particles that promote the formation of atherosclerotic lesions. Although *in vitro*, animal, and human studies have been published, questions that remain regarding cranberry's support of cardiovascular health include the optimal form, amount, and duration of cranberry bioactive consumption, the specific groups of people who may benefit most, and the mechanisms through which cranberry may act. A summary of relevant human clinical trials on cardiovascular health is presented below.

Healthy Adults

Conflicting results have been observed in trials conducted with healthy men and women in trials ranging from 2 to 16 weeks. In a 2-week uncontrolled trial, a decrease in ox-LDL-C without significant changes in plasma lipid levels was observed in a group of 21 men (mean age 38 years) who consumed a daily dose of 7 mL/kg body weight of cranberry juice (Ruel et al 2005). Similarly, no changes in lipids were reported in a 2-week controlled trial of 20 healthy women (mean age 28 years) who consumed 750 mL of cranberry juice compared to a placebo (Duthie et al 2006).

Several studies in healthy, sedentary men with elevated waist circumference have been published. In a 16-week study, a 4-week placebo juice phase was followed by increasing daily doses of low-calorie cranberry juice (125 ml/d, 250 ml/d, 500 ml/d) over three successive periods of four weeks (Ruel et al 2008). Favorable changes were observed for high-density lipoprotein cholesterol (HDL-C) and plasma ox-LDL-C with the 250 and 500 mL doses, and in markers of cellular adhesion with the 500 mL dose. There was no effect on total cholesterol, LDL-C, or triglycerides. With the same design, another study reported an increase in HDL-C with 250 and 500 mL cranberry juice, and no change in total, LDL, or VLDL cholesterol (Ruel et al 2006). Important drawbacks of both of these studies are that it is unclear whether the favorable changes in plasma ox-LDL-C or HDL were the result of increasing doses of cranberry juice or duration of the intervention, and there was no placebo control group. Finally, in a 4-week double-blind crossover study, 500 mL cranberry juice daily compared to placebo did not elicit an effect on arterial stiffness in this population (Ruel et al 2013).

Adults with cardiovascular risk factors

Randomized placebo-controlled studies of cranberry's cardiovascular health effects have been conducted in adults with cardiovascular risk factors. In a double-blind crossover study, the effects of cranberry juice on vascular function in 44 adults with coronary artery disease were examined (Dohadwala et al 2011). Participants were assigned to consume either 480 mL of low-calorie 54% cranberry juice or a matched placebo for four weeks followed by a 2-week washout period and consumption of the alternate beverage for four weeks. No effects of beverage consumption on serum lipids, blood glucose, insulin, or markers of inflammation were observed, except for a 1-mg/dL reduction in HDL cholesterol compared with a 1-mg/dL (2%) increase after placebo. Cranberry juice reduced a clinically relevant measure of arterial stiffness, although it is unknown whether this effect would persist with longer treatment or have any effect on cardiovascular disease risk.

A second study of 69 adults with peripheral endothelial dysfunction and CVD risk factors consuming 480 mL/day of 54% cranberry juice over four months reported no change in ox-LDL-C or lipids compared to placebo (Flammer et al 2012).

Although, there was no significant improvement in peripheral endothelial function over time, compared to placebo there was a reduction in circulating osteocalcin-positive endothelial progenitor cells (EPC), a characteristic of coronary endothelial function.

Finally, in a double-blind trial in women with metabolic syndrome who consumed 480 mL/day of cranberry juice for 8 weeks, there was a significant decrease in ox-LDL-C compared to the placebo (n = 15-16/group) (Basu et al 2011). Cranberry juice significantly increased plasma antioxidant capacity but caused no significant improvements in markers of inflammation (C-reactive protein and interleukin-6), blood pressure, glucose and lipid profiles. Limitations to this study include a small sample size and short treatment duration, therefore results are not generalizable.

Adults with diabetes

Diabetes is a potentially modifiable risk factor for CVD that may be affected by cranberry consumption. Two 12-week randomized, placebo-controlled trials using cranberry capsules report conflicting results (Lee et al 2008; Chambers and Camire 2003). In a double-blind study among 30 volunteers with Type 2 diabetes, mean age 65 years, and taking oral glucose-lowering medication, there were reductions in LDL-C, total cholesterol, and with total:HDL-C ratio with 1500 mg of cranberry extract powder (3 capsules/day) compared to placebo (Lee et al 2008). However, ox-LDL-C levels, fasting glucose, and glycated hemoglobin did not change in either group.

A similar study was conducted with 27 adults, mean age 56 years, who controlled their Type 2 diabetes through diet alone (Chambers and Camire 2003). There were no differences in fasting serum glucose, hemoglobin A_{1C}, fructosamine, triglyceride, HDL-C, or LDL-C levels after 6 or 12 weeks with 6 capsules/day of cranberry juice concentrate powder (equivalent to 240 mL of cranberry juice) compared to placebo.

Drug-Nutrient Interactions

Well-controlled, clinical pharmacokinetic and pharmacodynamic studies published in the 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 (Lilija et al 2007; Li et al 2006; Ansell 2009). An assessment of male subjects taking warfarin reported no significant interaction between the daily consumption of 250 mL of cranberry juice and warfarin (Li 2006). Additionally, a randomized, double-blind trial demonstrated no clinically relevant interaction between cranberry juice and warfarin, suggesting that "other factors were likely responsible for the findings in the anecdotal case reports (Ansell et al 2009)." Only one non-blinded, open-labeled clinical trial showed a modest increase in INR with 3000 mg of encapsulated cranberry juice concentrate in 12 healthy volunteers who were not already taking warfarin (Mohammed Abdul et al 2008).

Summary

More than 350 research and review articles have been published about cranberry and its nutritional and health benefits, cumulatively affirming that cranberries are a unique part of a healthful eating pattern. These studies include analytical, laboratory, and animal research, as well as human clinical trials. Understanding of how cranberry exerts health effects is evolving. Further research is needed to understand mechanisms of action, the impact of form, dose, and duration of cranberry consumption on physiological function and health outcomes, as well as the characteristics of individuals who may benefit most from cranberry consumption.

Additional references are available at the Cranberry Institute Web site, under the Cranberry Health Research Library at: www.cranberryinstitute.org.

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