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American Cranberries and Health Benefits – an Evolving Story of 25 years

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Abstract

Cranberries contain various type of bioactive components. Scientists have been studying cranberries' beneficial effects on urinary tract health since the 20th century. Entering the 21st century, the protection of cranberry phytochemicals against cancer and vascular diseases has drawn more attention from researchers. Anthocyanins, procyanidins, and flavonols in cranberries were all documented to have potential effects on cancer prevention. The cardiometabolic effects of cranberries have been investigated in several clinical trials. It was found that cranberries positively affect atherosclerotic cholesterol profiles and decreased several cardiometabolic risk factors. Nowadays, growing evidence suggests other important role of cranberries in maintaining digestive health. Cranberry juice or cranberries have been shown to inhibit the colonization of *H. Pylori* in stomach and protect against intestinal

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inflammation. For future research, clinical trials with improved study design are urgently needed to support cranberries' health benefits on urinary tract health and cardiometabolic diseases. Hypothesis-driven studies using animals or cell culture are needed to elucidate the mechanisms of cranberries' effects on digestive health.

Keywords: cranberries, catechin, procyanidin, urinary tract infection, health

INTRODUCTION

Cranberries, a fruit originally from New England are currently grown throughout the east and northeast parts of United States and much of Canada. Recorded folklore from 1600s showed that cranberries were used to treat urinary tract infections by the Native Americans. They were consumed as a food and used for wound and blood poisoning treatment(1). Research on the health benefits of cranberries started in the 1980s but intensified and evolved quickly in the last 25 years (Figure 1). Besides fruits, cranberry leaves were also used for urinary disorders, diarrhea and diabetes(2). Cranberries were later found containing various type of bioactives, mostly polyphenols, including proanthocyanidins, anthocyanins, flavonols and phenolic acids. Cranberries are among a few foods that contain A-type proanthocyanidins. Different from B-type proanthocyanidins, A-type proanthocyanidins have an additional ether interflavan bond between C2 $\rightarrow O \rightarrow$C7(3). It was suggested that A-type proanthocyanidins have greater bioactivity comparing to B-type(4).

Cranberry bioactives have unique characteristics and modern science are trying to identify the connections between cranberries' health benefits and specific compounds it contains. The

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most well-known health benefit of cranberries is the prevention of urinary tract infections (UTIs). However, due to the lack of persuasive clinical evidence, it is still something under discussion. A-type proanthocyanidins are thought to be able to inhibit binding of uropathogenic *E. coli* to the bladder which is an initial step for urinary tract infection(5-9). Two recently studies suggested that cranberry oligosaccharides might also play a role in preventing UTIs because xyloglucan oligosaccharides was found to be a new cranberry bioactive component with *E. coli* anti-adhesion activity(10, 11). The strong antioxidant and anti-inflammatory activity is another feature of cranberries, which is closely related to cancers and cardiovascular disease prevention. Cranberries are also found to improve lipid profile, improve endothelial function and lower several markers of cardiometabolic risk(12-14). Nowadays, growing evidence suggests an important role of cranberries in maintaining digestive health(15, 16). Two 250 mL bottles of cranberry juice daily for 90 days was found to suppress *H. pylori* infection in the stomach of susceptible populations(17). In addition to the anti-inflammatory effects, cranberries may also influence the intestinal barrier integrity, which is another essential element of intestinal health(18, 19). A new trend of study is exploring the effects of cranberries on gut microbiota composition(15).

Cranberry research from 1990s to 2000s: Urinary tract health

The folklore of cranberries' beneficial effects on urinary-tract health dated back to 1683 when the fruit was used in recipes(20). This plausible benefit was tested in many intervention trials but with inconsistent conclusions. The discrepancies between results partly due to differences in study population, sample size, lack of placebo control, and study compliance. In the late 1990s, Avorn et al. conducted the first robustly designed, randomized, double-blinded

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placebo-controlled trial(8). One hundred and fifty-three female subjects in a nursing home with an average age of 78.5 y were recruited for this 6-month trial. The study included relatively large number of participants and had relatively long duration of treatment. It showed that frequency of bacteriuria was reduced by more than 50% following daily consumption of 300 mL low calorie cranberry juice cocktail. The placebo drink used in this study was reported to be indistinguishable in taste, appearance, and vitamin C. This result indicated potential beneficial effect of cranberry juice on urinary tract health. Another randomized double-blinded placebo-controlled cross-over study conducted by Walker et al. showed similar positive results(21). Statistically significant reduction of UTIs risk was found with 10 out of 19 subjects aged from 18 to 45 y. Different from the previous study, subjects were given two 400 mg capsules of cranberry powder to consume once per day for 3 months. In addition, four other studies have obtained successful primary outcomes supporting the beneficial effect of cranberry juice on urinary tract health even though they all had design limitations(22-25).

In the early 2000s, Kontiokari et al(26)and Stothers et al(27) investigated the effects of cranberry juice or tablets on UTI prevention, respectively. The subjects were healthy, sexually active women, aged 21-72 y, with a history of UTI. Both studies showed a significantly decreased number of patients experiencing at least one episode of UTI per year. In a very recent randomized, double-blind, placebo-controlled, multicenter clinical trial(28) , 373 healthy women with a recent UTI history were recruited to consume 240 mL low calorie cranberry juice cocktail daily for 24 weeks. Cranberry juice consumption significantly reduced the number of UTIs by 39%. The rate of clinical UTI with pyuria episodes was reduced by 37%. This was the largest clinical trial to date and properly designed to have greater statistical power. The

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compliance rate was much higher compared to previous studies with 98% and 86% in the cranberry and placebo group, respectively.

UTI is a common bacterial infection in children(29). Several pediatric trials have been conducted in early 2010s to evaluate whether cranberry juice consumption prevent the recurrences of UTI in children. The subjects recruited in these studies were healthy children including both females and males, aged 1-18 years, with a history of recent UTI. One serving of 50 mL cranberry juice were given to children to drink once per day for 6 months(30). The incidence of UTIs in cranberry group was 18.5% compared to 48.1% in the control group, demonstrating a significant reduction in the risk of recurrent UTIs following cranberry juice consumption. This trial had a relatively large sample size (n=84) and low dropout rate, 3.5% in cranberry group versus 6.8% in control group. Cranberry juice with or without proanthocyanidins were randomly assigned to 40 children for one year(31). A 65% reduction in the risk of UTIs was obtained during a 12-month follow-up. The compliance level was 70% for both groups. Both studies suggested that cranberry juice were effective in preventing the recurrence of pediatric UTI. Salo et al.(32) conducted a double-blinded randomized placebo-controlled trial in 2012. Two hundred and sixty-three children drank cranberry juice or placebo for 6 months. The study showed that cranberry juice consumption reduced the number of UTI recurrences by 43% and the number of days on antibiotics.

Several meta-analysis reviews have been conducted to assess the effectiveness of cranberry products in preventing UTIs in susceptible populations. A 2008 Cochrane review(33), which included five cross-over and five parallel designed studies, reported that cranberry products significantly reduced the incidence of UTIs at 12 months compared to placebo/control

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group. Cranberry-containing products was found to be associated with preventative effects on recurrent UTIs in another systematic review of 13 randomized controlled trials(34). The most recent meta-analysis and trial sequential analysis evaluated 28 clinical trials and concluded that the use of cranberry products significantly reduced the incidence of UTIs(35). However, meta-analysis in the 2012 Cochrane review(36) concluded that cranberry products did not significantly reduce the occurrence of symptomatic UTI overall compared to placebo, water, or no treatment. This review had substantial heterogeneity in the results.

Several factors attribute to the conflicting results obtained from clinical trials. Low compliance due to astringency and bitterness of cranberry juice, high withdrawal rate, inconsistency of dosage, lack of standardization of cranberry content in testing products are the major factors. Cranberry capsules were used to overcome the undesired taste of cranberry juice. However, in two trials using cranberry capsules, the withdrawal rates were more than 40% partly due to the side effects(37, 38). Quite a few trials are not randomized, double-blinded, placebo-controlled or short duration time (less than 6 months). In addition, the optimum dosage and formulation were not established in previous studies(39).

Along with the struggle of searching for ideal study design in cranberry and UTIs researches, in the 21st century, researchers begin to switch their attention to other health benefits.

The new trend started with the antioxidant activity of anthocyanins in cranberries. It was shown that over 50% of the oxygen radical scavenging capacity of cranberries was attributed to anthocyanins(40). Antioxidant properties play an important role in protection

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against cancer and vascular diseases. Besides anthocyanins, cranberries are rich in flavonoids like proanthocyanidins and flavonols, which also have potential effects on cancer and cardiovascular diseases. Quercetin counts for more than half of flavonols in cranberries(41). It was reported that quercetin inhibited growth of human cancer cells(42, 43). Together with anthocyanins, quercetin glycosides extracted from cranberries had comparable antioxidant capacity to vitamin E(44). There is a growing interest in the structure and activity of proanthocyanidins in cranberries. Later study showed that proanthocyanidins fraction isolated from cranberries inhibited the growth of lung cancer cell(45). A recent review(46) on the topic of cranberries and cancer suggested that cranberry bioactives exert chemoprevetion by affecting cancer cellviability, proliferation, adhesion, kinetics, apoptosis, signaling pathways, oxidative status and inflammation. Results from several studies suggested cranberry juice extract, cranberry proanthocyanidin-rich fraction and flavonoid-rich fraction decreased the cell viability or density of 41 cancer cell lines of 16 types(47-58). As mentioned, cranberries are among a few foods that contain A-type proanthocyanidins and A-type proanthocyanidins are thought to have greater bioactivity comparing to B-type(4). However, besides the anti-adhesion activity of uropathogenic bacteria, whether A-type proanthocyanidins have other unique health benefits was unknown. Degree of polymerization of proanthocyanidins is another issue that needs to be considered because it significantly influences their bioavailability. It was found that proanthocyanidins dimers and trimers were transported and absorbed *in vivo* whereas larger oligomers or polymers were not absorbable(59). Cranberry A-type proanthocyanidin dimers, trimers, and tetramers transported across human epithelial colorectal adenocarcinoma cells (Caco-2 cells) monolayer at low rates, suggesting that they could be absorbed by humans(60).

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More studies are needed to determine whether proanthocyanidins with different degree of polymerization have distinguishable health benefits. Any possible synergistic effects between cranberry oligosaccharides and A-type proanthocyanidins also needs to be explored.

Cranberry research from 2010 to present: Cardiometabolic effects and intestinal health

Cardiometabolic effects of cranberries have drawn attention from researchers in the 2000s and became a focus in the 2010s. According to a review paper published in 2016(61), fourteen clinical trials have been conducted during 2005 to 2015 to explore the cardiometabolic effects of cranberries. Interestingly, among them, six out of seven clinical trials conducted before 2011 were open labeled while six out of seven conducted after 2011 had randomized placebo-controlled design, which suggested the design of these cranberry intervention trials has improved. These studies with different study design also varied largely in results. Many studies evaluated the lipid profile of participants. Ruel et al. conducted a series of open-labeled studies from 2005 to 2008(62-64). Their first study (64) in 2005 on health men with an average age of 38 y suggested there was no change in low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol levels. However, their latter two studies(62, 63) in healthy sedentary men with an average age of 51 y showed increase in HDL cholesterol, decrease in LDL cholesterol and decrease in the ratio of total cholesterol to HDL cholesterol, indicating an improvement of lipid profile. In 2015, Novotny et al.(14) conducted a placebo-controlled trial among healthy adults with an average age of 50 y showing that there was no significant difference in LDL cholesterol and HDL cholesterol levels between control and treatment groups. The other two placebo controlled studies, one among adults with type 2 diabetes(13), one among adults with cardiovascular disease risk factors(65), both showed no

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significant change in LDL cholesterol and HDL cholesterol levels after cranberry juice consumption. The inconsistent results and the variance of these researches in study design make it difficult to identify if cranberries have effects on human blood lipid profile.

In addition to lipid profile, researchers were interested in the improvement of endothelial function after cranberry consumption. A placebo-controlled crossover study of Dohadwala et al.(66) found there was no improvement in flow-mediated dilation or peripheral artery tonometry after double strength (540 g kg^-1) cranberry juice consumption (480 mL per day) for 4 weeks among patients with coronary artery disease. Similarly, a double-blinded randomized study of Flammer et al.(65) found no significant changes in peripheral artery tonometry among individuals with endothelial dysfunction after double strength (540 g kg^-1) cranberry juice consumption (460 mL per day) for 4 months. However, a recent study in 2016 got some interesting results. Rodriguez-Mateos et al. correlated the cranberry polyphenol metabolites with improvements in vascular function(67). They carried out a double blinded randomized placebo controlled crossover study and observed dose-dependent increases in flow-mediated dilation 8 hours after cranberry juice (250 g kg^-1, 480 g kg^-1, 760 g kg^-1, 940 g kg^-1, 1170 g kg^-1) consumption among healthy adults. This study went further to identify and quantitate individual metabolites of cranberry polyphenols. Among the 60 metabolites they have identified in plasma, twelve metabolites significantly correlated with the increases in flow-mediated dilation. This may become a trend of future studies: exploring the change of metabolic profiles in biological fluids after cranberry consumption.

Glucose regulation is another important aspect of cardiometabolic health. But similar to the lipid profile and endothelial function, studies so far give very discordant results. Four

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studies(68-70) showed favorable glycemic responses after cranberry products consumption while the other two(13, 71) showed no significant effects. They had different study design and conducted among different population with different size of population, which made the interpretation of these data difficult.

A new trend of cranberry study is exploring the effect of cranberry on intestinal health. According to the searching results from PubMed, when using "cranberry" and "intestinal" in title/abstract as searching words, there are 26 publications in 2011-2017 comparing to 8 publications in 2000-2010. Searching Web of Science using "TS=cranberry AND TS=intestinal" yielded 16 publications in 2000-2010 comparing to 41 publications in 2011-2017. Unlike the studies about urinary tract or cardiometabolic health are human studies in the form of clinical trials, currently most cranberry studies in intestinal health are performed on animal or cell culture models. Two aspects of cranberries' influence on intestinal function have been studied: preventing intestinal inflammation and improving gut microbiota profile. Anti-inflammatory activity of cranberry was found in 2009. A study showed that cranberry proanthocyanidins attenuated the bacterial lipopolysaccharide -induced expression of iNOS and COX-2 in macrophages(72). Later on, a feeding study on rats found that pro-inflammatory cytokines such as interleukin IL-1β, IL -6 were significantly lower and the anti-inflammatory IL-10 was higher in cranberry powder treatment group(73). A study published in 2014(15) also showed that cranberry extract protected mice from high-fat high-sucrose diet induced intestinal inflammation by increasing *Akkermansia* spp. population. Eight-week-old mice were divided into 3 groups, one received normal chew diet and gavaged with vehicle (water) for 8 weeks; two groups received high-fat high-sucrose diet, one group gavaged with cranberry extract (0.2 g

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kg^-1), the other one group gavaged with vehicle for 8 weeks. According to their results, cranberry extract lowered intestinal triglyceride content, and alleviated intestinal inflammation and oxidative stress. The highlight of this study was the correlation between the beneficial effects of cranberries with improved gut microbiota profile. In the past, cranberries were well-known for its antiadhesion activity against various microbial species in different organs (oral cavity, stomach, small intestine and colon(74-78)). This study showed that it also prevented intestinal inflammation by increasing certain bacteria population. *Akkermansia* was found to reduce systemic lipopolysaccharide levels in high fat fed mice(79). This may explain its protective effects against intestinal inflammation. The prevalence of inflammatory bowel disease (IBD) and its associated risk of colon cancer have drawn attention over the past decade. Xiao et al.(80) found that a cranberry extract (composed of phenolics and cranberry fiber) and dried cranberries reduced disease activity index among experimental colitis mice induced by dextran sodium sulphate (DSS). Dried cranberries preserved colon length and decreased serum pro-inflammatory cytokines (TNF-α, IL-1β) levels. Interestingly, dried cranberries showed greater protection activity against colitis than cranberry extract and 5-aminosalicylic acid which is an anti-inflammatory drug used to treat IBD.

Denis et al.(16) conducted a study of cranberry bioactives specially focusing on inflammation, oxidative stress and mitochondrial dysfunction in the intestine. Distinguishing from previous studies, this study used different cranberry phenolic fractions as experimental groups. They obtained three molecular mass fractions in terms of phenolic acid, flavonoid, procyanidins and total phenolics: low molecular mass cranberry polyphenols (rich in phenolic acid); medium molecular mass cranberry polyphenols (rich in anthocyanins, flavonols and

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procyanidin dimers); high molecular mass cranberry polyphenols (rich in flavonols and procyanidins dimers, oligomers and polymers). According to the profile provided in the paper, low molecular mass fraction had some phenolic acids and proanthocyanidin monomers. Medium molecular mass fraction contained relatively high amount of anthocyanins, flavonols and some proanthocyanidin dimers. High molecular mass fraction was rich in dimers, oligomers and polymers of proanthocyanidins, also had high amount of flavonols. To study cranberries antioxidant and anti-inflammatory activity, they seeded Caco-2 cells on porous filters (Transwell) to form monolayer and treated cells with cranberry fractions with or without pre-treatment of lipopolysaccharide or iron and ascorbic acid. They found that all three fractions maintained the level of TNF-α and IL-6, COX-2 comparing to control group. They also explored molecular mechanisms on whether cranberry bioactives could blunt the activation of NF-κB signaling pathway. The results suggested that comparing to control group, these three fractions significantly decreased NF-κB to IκB protein ratio after lipopolysaccharide treatment, indicating the inhibition of NF-κB signaling pathway by these cranberry fractions. But this study also suffered from limitations. There was large overlaps of chemical compounds between these fractions. Flavonols were present in both medium molecular mass and high molecular mass fractions while anthocyanins were present both in low molecular mass and medium molecular mass fractions. Each fraction was a mixture of different polyphenol compounds, therefore making it hard to find which type of polyphenol compound played the most important role in anti-inflammation.

Moreover, cranberry proanthocyanidins were found to improve the mouse intestinal health by increasing luminal secretory immunoglobulin A, which is the primary protective

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compound of mucosa and can exclude bacteria from attachment(19). It was shown that cranberry proanthocyanidins had anti-adhesive activity against extra-intestinal pathogens(81, 82), like E.coli. These studies shed a light on the possibility that cranberry may improve intestinal health by enhancing intestinal barrier function. Currently, there is very limited research published in this area. But one study(18) has shown that pure (-)-Epicatechin prevented TNF-α -mediated Caco-2 cell barrier permeabilization by inhibiting NF-κB activation and downstream tight junction protein, like ZO-1 protein disruption. Since it has been demonstrated that cranberry inhibit LPS-induced activation NF-κB pathway and decrease the level of TNF- α, it is reasonable to hypothesize that cranberry also promote the tight junction protein expression and therefore enhance intestinal barrier integrity.

FUTURE DIRECTION

Progresses in three areas are needed for the future research of cranberries. First, clinical trials with better design including longer treatment time, sufficient bioactive compounds, and proper compliance verification are needed to determine the effects of cranberry products on UTI. High dropout rate and lack of compliance verification plagued nearly all previous clinical trials. Several metabolomics studies have been published in collective efforts to identify biomarkers of cranberry consumption for compliance verification(83-85). Secondly, bioactive compounds in cranberries that are responsible for preventing UTI need to be identified and mechanism elucidated. A-type proanthocyanidins from cranberries inhibited the adherence of uropathogenic *E. coli in vitro(82),* however, their concentrations in urine were too low to have such effects. Human urine after cranberry juice consumption, but not grape, chocolate, apple, or tea consumption, was able to inhibit bacterial adhesion(4). But it was unknown which

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compounds in urine were responsible. It is reasonable to assume some microbial metabolites of A-type proanthocyanidins may have anti-UTI activity. Recent metabolomics studies showed that administration of cranberry extracts in rats cause significant change of metabolome in the urine(83, 84). A number of putative biomarkers were identified. The correlation between antiadhesive activity and metabolomics changes suggested that alterations in urinary metabolome were partially responsible for anti-UTI activities(83). Thirdly, studies are needed to illustrate how cranberry consumption affect the composition of microbiota in both gut and urinary tract. The female urinary tract harbors a unique bacterial community that is different from and plausibly affected by microbiota in the gut. Remarkable differences in microbiome in urinary tract were identified between healthy women and those with urologic diseases(86). Cranberry extract is known to affect microbial composition in the gut of mice(15), however it unknown whether or how cranberry consumption will affect gut microbiota in human. If gut microbiota were affected by cranberry in diet, it is reasonable to assume that this will lead to changes of microbiota in urinary tract. Research findings in the area will provide missing pieces of a puzzle on how cranberry consumption affect urinary health.

CONCLUSION

The focus of cranberry research on human health evolved from urinary tract health, cancer, to cardio metabolic diseases in the past 25 years. There is a new trend to investigate how cranberry consumption affect digestive health and gut microbiota. Future research of cranberries should focus on clinical trials with better experimental design and compliance control, identification of bioactive compounds in cranberries or metabolites of cranberries and

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their mechanisms of action, and influence of cranberry consumption on both gut and urinary tract microbiota.

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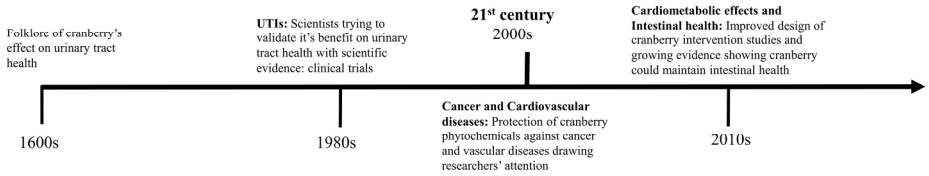

Figure 1. Timeline of cranberry research

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