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Review

Evidences of the cardioprotective potential of fruits: The case of cranberries

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Eating a healthy balanced diet, is one of the most important and relevant ways to delay and prevent various health complications including cardiovascular disease (CVD). Among the nutritional factors that have been investigated in recent years, dietary fat intake may be the one that has been most targeted. However, there is also clear epidemiological evidence that increased fruits and vegetables intake can significantly reduce the risk of CVD, an effect that has been suggested to be resulting to a significant extent, from the high polyphenol content of these foods. Numerous polyphenolic compounds such as flavonoids have been identified as having strong antioxidant properties. Most interesting is the fact that, in addition to being one of the largest groups of antioxidant phytochemicals, flavonoids are also an integral part of the human diet as they are found in most fruits and vegetables. Cranberries are one of the most important sources of flavonoids that have a strong antioxidant and anti-inflammatory capacities. Thus, consumption of cranberries or their related products could be of importance not only in the maintenance of health but also in preventing CVD. The following review will present evidences supported for the most part by clinical observations that cranberries can exert potentially healthy effects for your heart.

Keywords: Cranberries / Cardiovascular disease / Flavonoids / Polyphenols

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1 Introduction

"*Let your food be your medecine and medecine be your food.*" – Hippocrates (460–370 BC)

Never have these words been so much at the heart of nutrition research than today. Increasing knowledge about the health effects of foods and their components, has led to numerous breakthroughs supporting the importance and relevance of consuming a healthy balanced diet to delay, prevent and even treat chronic diseases [1–3]. Such concepts as the polymeal [4] or the portfolio diet [5] have been suggested to reduce cardiovascular disease (CVD) risk by as much as 75%. From the work of fundamental and clinical researchers of the last decade have emerged research areas like functional foods and nutraceuticals based on the notion that eating healthy foods brings added benefits to body functions beyond their traditional nutritional value. Although most chronic diseases (*e.g.* heart disease, diabetes, cancer) all have, to some extent, a genetic influence, most of them only develop if favorable environmental conditions prevail, and this is certainly the case for CVD, the leading cause of death around the world [6, 7]. Among those environmental influences, health professionals and researchers have established over the years that CVD can be prevented by adopting an active lifestyle and having healthy nutritional habits [8, 9]. Indeed, regular physical activity is associated with numerous metabolic improvements that range from more efficient cell signaling to mechanical and physiological adaptations helping the body to be more efficient and protect itself from CVD. On the other hand, sedentariness favors the development of obesity and numerous metabolic alterations that lead to CVD [6, 7]. Epidemiological studies have led to the identification of nutrition as a key component for the maintenance and promotion of cardiovascular health and the important role of fruits and vegetables consumption in that relationship is suggested [2]. The task is now to give support to epidemiological evidence

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Abbreviations: **CJ**, cranberry juice; **CVD**, cardiovascular disease; **OxLDL**, oxidized LDL particles

through small- and large-scale intervention trials. The current review will present evidences some of which supported by recent clinical observations and showing that the consumption of cranberries *(Vaccinium macrocarpon)*, a fruit rich in polyphenolic compounds could be good for your heart.

2 Risk factors for CVD: From tradition to innovation

Multiple epidemiological studies have shown that there is a significant positive relationship between blood cholesterol levels and mortality from heart disease. For instance, randomized clinical trials from the past 20 years have firmly established that LDL-cholesterol reduction is a key factor in preventing CVD [10–15]. In contrast, a reduced circulating HDL-cholesterol concentration is associated with an increased risk of CVD while increasing HDL-cholesterol is considered to be cardioprotective [16–18]. Other metabolic parameters have also been the topic of thorough investigation and have been identified as strong independent risk factors for CVD. In this regard, the simultaneous presence of hyperinsulinemia, elevated apolipoprotein (apo) B and small dense LDL particles, conditions often found in hypertriglyceridemic subjects and which are features of the metabolic syndrome, has been associated with a 20-fold increase in the risk of ischemic heart disease [19].

However, it appears that alterations in plasma lipoprotein-lipid concentrations are not the only factor to consider when assessing heart disease risk. In fact, there is increasing evidence showing that the inflammatory response of vascular cells to different stimuli (*e. g*. oxidative stress and hyperlipidemia) leading to endothelial dysfunction also needs to be considered in the development of CVD [20]. In this regard, free radicals or reactive oxygen species (ROS) are produced continuously in humans through a number of cellular events including energy production and detoxification of the body, or generated by exhaustive exercise [21]. Although free radicals are important mediators of cell signaling, they also have the capacity to alter the integrity of numerous molecules such as lipids, proteins and DNA [22]. Fortunately, nature has provided humans with defense mechanisms directed at counteracting these generated ROS and limit the oxidative damage they can induce. Numerous endogenous (mostly enzymes) and exogenous (diet-derived or drugs) antioxidant substances play a major role in the body defense system against oxidation [23] and therefore must be considered important in the maintenance of health. These include enzymes like the superoxide dismutase (SOD), glutathione peroxidase (GPx) and the HDL-associated paraoxonase (PON)-1 as well as molecules like vitamins (A, C and E), flavonoids and statins. These antioxidants have a broad spectrum of activities including scavenging of free radicals, chelation of transition metal ions, sparing of other antioxidants such as vitamin E and carotenoids and preservation or increase of the activity of paraoxonase [24–26].

Oxidative stress is a widely used and ill-defined term that refers to the imbalance in the rate at which the intracellular content of ROS increases relative to the capacity of the cell to dispose of these free radicals, most likely due to insufficient antioxidant reserves or intake. Aging, illnesses, demanding physical tasks, as well as cancer and chronic inflammatory diseases [27–30] are all conditions associated with an increased oxidative stress. In addition, non-insulin dependent diabetes mellitus (NIDDM) or type 2 diabetes [31] and impaired lipid metabolism [32] are associated with oxidative stress, which is believed to be a pathway through which atherosclerosis develops in insulin-resistant and dyslipidemic individuals. It has been shown that oxidized LDL particles (OxLDL) promote macrophage foam cell formation, which is the predominant cell type in the earliest atherosclerotic lesions known as fatty streaks [33]. In this regard, the circulating OxLDL level has been found to be useful a marker for identifying patients with coronary artery disease [34–37].

Vascular endothelial cells have long been considered as inactive and only acting as a semipermanent barrier between blood and tissue [38]. However, numerous evidences now support an important role of the vascular endothelium in maintaining homeostasis in humans. For instance, functions of the endothelium include the maintenance of blood circulation and fluidity as well as regulation of vascular tone. When activated, endothelial cells express a large selection of proteins including adhesion molecules such as the intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) that are involved in the modulation of leukocyte recruitment and platelet adhesion during thrombosis and inflammation [39]. Endothelial activation can be triggered by inflammatory stimuli, which include free radicals, inflammatory cytokines and exposition to OxLDL particles [33]. In healthy individuals, activation of endothelial cells is temporary and its duration will be affected by the intensity of the inflammatory stimulus. However, high concentrations of soluble ICAM-1 and VCAM-1, that can be measured in plasma [40], probably as a result of shedding from the surface of activated endothelial cells [41], have been found in diabetic, hyperlipidemic and abdominally obese individuals [42–45]. Chronic activation of the endothelium, often referred to as endothelial dysfunction, plays an integral role in the development of atherosclerosis and CVD [33].

There are now many markers available for the prediction of CVD events and the refinement of the different variables of the risk profile give researchers and clinicians different avenues to understand CVD as well as offer numerous targets for interventions to prevent and treat CVD.

3 Nutrition and chronic diseases

As indicated above, eating a healthy balanced diet is considered a relevant way to delay and prevent various health complications including heart disease [1 – 3]. Among the nutritional factors that have been investigated over the years, dietary fat intake may be the one that has been most targeted and recommendations now include the replacement of saturated (SFA) and *trans* fatty acids with mono (MUFA) and polyunsaturated fatty acids (PUFA) in the daily diet. Favorable changes partly responsible for the reduction of heart disease associated with n-3 PUFA consumption include a hypolipidemic effect as well as the attenuation of inflammatory and endothelial responses, hypercoagulability, fibrinolytic resistance and altered platelet activation [46]. The anti-inflammatory action of unsaturated fatty acids *in vitro* has been recently suggested to result from the inhibitory effects of n-3 PUFA on nuclear factor kappa B (NF-κB) activation via a PPARα-dependent pathway [47].

Several epidemiological studies [2] have associated a high consumption of fruits and vegetables with a decrease in the risk of CVD, an observation that is also supported by recent results from the INTERHEART Study [48]. Consumption of fruits and vegetables has also been suggested to provide some explanation for the cardioprotective effect of the Mediterranean diet even in the absence of significant changes in plasma lipids [49]. Numerous mechanisms have been suggested to explain the beneficial impact of fruits and vegetables on cardiovascular health. However, the one that has attracted most attention is their high content in the polyphenolic compounds called flavonoids. These molecules have been known as plant pigments for over a century and are implicated in different processes that include plant growth, reproduction, seed germination as well as resistance to pathogens and predators [50]. Moreover, flavonoids are characterized by an antioxidant activity, which differs depending on their structure, but that is crucial in the protection of DNA from UV light and other sources of oxidative stress [50]. Briefly, the common structure of flavonoids is composed of diphenylpropane (C6-C3-C6) consisting of two aromatic rings linked by a six-member ring. Flavonoids can be further divided into six major classes, based upon variations in the central ring, *i. e*. flavones, flavonols, flavanones, catechins, anthocyanidins and isoflavones [51]. Supportive of their cardioprotective potential, flavonoid intake has been related to decreased morbidity and mortality from CVD, which has been suggested to be the result, to a significant extent, of their antioxidant activity that inhibits oxidation of LDL particles [52].

Epidemiological evidence also indicates that a high intake of antioxidants substances like carotenoids and/or vitamin C, which are present in fruits and vegetables, is associated with a lower incidence of CVD [53 – 56]. However, intervention trials aimed at supplementing individuals with carotenoids and/or vitamin C have failed to show a strong impact on CVD risk [57, 58].

Table 1. Nutritional composition of raw cranberries[a)]

	Cranberries (raw) *Vaccinium macrocarpon*
Per 100 g	
Energy (Kcal)	46
Energy (kJ)	194
g per 100g	
Water	87.13 ± 0.28
Carbohydrates	12.20
Fibers	4.6 ± 0.12
Lipids	
Total	0.13 ± 0.03
Saturated	0.011
Monoinsaturated	0.018
Polyinsaturated	0.055
Proteins	0.39 ± 0.10
Ash	0.15 ± 0.03
mg per 100g	
Minerals	
Calcium	8.00 ± 0.36
Iron	0.25 ± 0.05
Magnesium	6.00 ± 0.13
Potassium, K	85.0 ± 2.5
Vitamins	
Vitamin C	13.30 ± 1.24
Vitamin A (IU)	60 ± 5
Vitamin E (α-tOH)	1.20 ± 0.12
Vitamin K	5.10 ± 0.45

a) From the United States Department of Agriculture (USDA) National Nutrient Database for Standard Reference http://www.nal.usda.gov/fnic/foodcomp/cgi-bin/list_nut_edit.pl. Values are presented as means ± SD. Keyword: raw cranberries.

4 Cranberry composition

Cranberries are one of the most important source of flavonoids and especially of the flavonols myricetin and quercetin [59, 60] that have been characterized with a potent antioxidant capacity. Accordingly to United State Department of Agriculture (USDA) National Nutrient Database for Standard Reference (http://www.nal.usda.gov/fnic/foodcomp/search/), cranberries (*Vaccinium macrocarpon*) are largely constituted of water (87% w/w) with carbohydrates accounting for approximately the balance of its weight (12%; Table 1). Despite not having an important fat content, the high proportion of n-3 long-chain fatty acids in berries makes them an important proportion of the daily intakes in some populations [61]. The list of other macro and micronutrients found in cranberries is also shown in Table 1.

As far as cranberry antioxidants are concerned, they mostly come under the form of phenolic acids [62] and fla-

Table 2. Flavonoid content of raw cranberries[a)]

	Cranberries (raw) *Vaccinium macrocarpon*	
mg per 100g	Mean ± SD	Low – High
Anthocyanidins		
Cyanidins	41.81 ± 2.86	32.16 – 53.35
Delphinidin	7.66 ± 1.93	0.12 – 10.66
Malvidin	0.31 ± 0.22	0.00 – 1.34
Peonidin	42.10 ± 3.64	32.56 – 58.18
Flavan-3-ols		
(–)-Epicatechin	4.37 ± 0.93	2.95 – 5.72
(–)-Epigallocatechin	0.74 ± 0.28	0.00 – 1.79
(–)-Epigallocatechin 3 gallate	0.97 ± 0.48	0.00 – 2.86
(+)-Catechin	0.39 ± 0.16	0.00 – 1.06
Flavonols		
Kaempferol	0.09 ± 0.03	0.00 – 0.27
Myricetin	6.78 ± 1.67	0.40 – 23.00
Quercetin	15.09 ± 0.13	7.30 – 25.00

a) From the United State Department of Agriculture (USDA) [60].

vonoids [63] at proportions of 44 and 56%, respectively, based on total dry weight of non-nutrient antioxidants [64]. Among the 15 phenolic acids identified in cranberries [65], benzoic acid is the most abundant [64, 65] while cranberry flavonoids are anthocyanidins, flavonols (quercetin and myricetin) and proanthocyanidins [63, 64, 66–67] (Table 2). Furthermore, cranberry juice (CJ) has also been shown to be a source of resveratrol in comparable proportion to what is found in grape juice [68].

5 Bioavailability of cranberry flavonoids

Flavonoids are absorbed at the intestinal level [69] at a rate of absorption that varies with respect to numerous factors such as the kind of flavonoids, co-ingestion of certain macro or micronutrients and the linkage of flavonoids to sugars. Indeed, glycosylated flavonoids are more efficiently absorbed than aglycone and the intestinal Na+/glucose cotransporter (SGLT1) has been suggested to explain most of this difference [70, 71]. Glycosylated flavonoids have also been shown to reduce glucose absorption in animals, suggesting a competition between both molecules for the SGLT1 receptor [72]. However, quercetin, one of the most important flavonoids in cranberries, has been found to be mostly of the glucuronidated [73] or sulfated [69] forms when in plasma, suggesting that flavonoid must go through glucuronidation of sulfation before entering blood vessels. An important part of the flavonoids that are absorbed by the intestine are brought back to the intestinal lumen via the multi-drug resistance protein-2 (MRP-2) while clearance of flavonoids from the circulation implicates the MRP-3 [69]. Furthermore, intestinal flavonoids absorption can be increased by numerous factors such as co-ingestion with a high-fat meal [74, 75]. Overall, it is estimated that only 5% of the ingested flavonoids reach circulation with the flavanols being the more easily absorbed [75]. Flavonoids that are unabsorbed by the small intestine are believed to be undergoing microbial degradation in the large intestine [76]. Interestingly, some of the microbial metabolites have been suggested to have potential cardioprotective effects, *e.g.* hydroxyphenylpropionic acid, a product of flavonol degradation, would inhibit platelet aggregation [51]. However, flavonoids and resveratrol have been found difficult to isolate and measure in plasma [77, 78], as they are known to tightly bound to proteins in circulation as well as to membranes of red and white blood cells and platelets.

On the other hand, several free phenolic acids are found in human plasma following CJ consumption [79]. Benzoic, ferulic and sinapic acids were found in plasma of humans from 45 up to 270 min after consumption of CJ. Phenolic acids are also identified in plasma but are not present in significant quantity in CJ, suggesting they could be metabolites from other phenolics from cranberries. An increase in plasma vitamin C levels [80, 81] was also noted as well as an increase in plasma total antioxidant capacity following CJ intake [80, 82]. However, CJ consumption failed to acutely increase endogenous antioxidants [81] or to suppress F2-isoprostane formation, a product of lipid peroxidation, *in vivo* [83]. Finally, evidence for the presence of salicylates in human plasma after CJ consumption has also been recently reported [84].

6 Cranberries and health

Clinical and epidemiological evidence have already shown that regular CJ consumption may help prevent [85–87] and even reduce [85] urinary tract infections (UTI), *i.e.* presence of microorganisms in the bladder, prostate and kidneys [88, 89]. The physiological mechanisms underlying the cranberry-related protection against UTI do not appear to involve flavonols but rather other cranberry constituents like fructose [90] and proanthocyanidins [91, 92] that inhibit bacterial adherence to mucosal surfaces. The antibacterial effects of cranberries have also been suggested to have possible benefits on gastric and dental health [93].

On the other hand, cranberries have been suggested to have a beneficial impact on cardiovascular health [94] and the following sections will try to review these effects, which are supported by clinical observations.

7 Effects of blood lipids

Until now, only a limited number of studies have investigated the effects of cranberries on blood lipoprotein-lipid levels in humans. Table 3 summarize the details relevant to these

Table 3. Human intervention studies on the cardiovascular health benefits of cranberry juice

Studies	Subjects	Dose (Duration)	Results
Pedersen, C. B. *et al.* [80]	9 women	500 mL	Increase in plasma TAC[a)]
Chambers, B. K. and Camire, M. E. [97]	12 diabetic men 15 diabetic women	6 capsules CJ powder equivalent to 240 mL/day (12 weeks)	No effect on plasma lipids
Duthie, S. J. *et al.* [81]	20 women	750 mL/day (2 weeks)	Increase in plasma TAC. No effect on plasma lipids. No effect on antioxidant enzymes. No effect on DNA oxidation
Ruel, G. *et al.* [82]	21 men	7 mL/kg body weight (14 days)	Increase in plasma TAC. Decrease in plasma OxLDL. No effect on plasma lipids
Ruel, G. *et al.* [96]	30 men	125, 250 and 500 mL/day (3×4 weeks)	Increase in plasma HDL-cholesterol. Decrease in plasma NOx[b)]

a) TAC, total antioxidant capacity.
b) NOx, nitrates and nitrites.

studies. Duthie *et al.* [95] found that supplementing healthy premenopausal women with 750 mL/day of CJ for a period of 2 weeks had no effect on circulating lipoprotein-lipid levels. We also reported that consuming ~700 mL of low-calorie CJ cocktail for 2 weeks failed to alter plasma lipid concentrations in men [82]. However, we also recently showed that HDL-cholesterol levels were increased in overweight men following low-calorie CJ consumption for a period of 12 weeks [96], which raises the possibility that in addition to the amount of juice consumed, duration of treatment, as with many other nutritional and behavioral interventions, may be an important determinant of the lipoprotein-lipid profile response to CJ consumption. In another study in diabetic patients, Chambers and Camire [97] reported no change of plasma lipoprotein-lipid levels after consumption of CJ concentrate powder capsules equivalent to 240 mL of CJ/day for a period of 12 weeks. However, the possibility that heat processing necessary to convert the cranberry concentrate to a powder had altered its bioactivity was raised by the authors as a possible explanation for their results.

In our studies, the increase in HDL-cholesterol concentrations in response to the intervention was mostly explained by the change in plasma apoAI concentrations which explained almost half (~48%) of the variation of HDL-cholesterol concentrations during the course of the intervention. This relationship could reflect an increase in the synthesis of apoAI comparable to the one reported following consumption of other flavonoid-rich foods like red wine [98]. *In vitro* evidences also suggest that cross-linking between oxidized apoAI molecules can impair their role in reverse cholesterol transport [99], and a potential reduction in apoAI oxidation following CJ consumption could have contributed to an increase in plasma HDL-cholesterol concentrations in our study. Furthermore, quercetin, a flavonol highly present in cranberries and its juice [100], has been shown to increase the expression of the HDL-associated enzyme PON-1 [101]. This effect not only confers to HDL particles a greater antioxidant activity, but also considering that PON-1 is a stimulant of macrophage cholesterol efflux [102] and reverse cholesterol transport, could also explain the increase in circulating HDL-cholesterol levels. A possible indirect effect of cranberries antioxidants on the activity of the adenosine triphosphate-binding cassette transporter A1 (ABCA-1), a protein closely implicated in the release of cholesterol from macrophages to HDL [103], cannot be excluded. Indeed, antioxidants present in cranberries have been shown to increase salicylates in urine and plasma [84] and it has been demonstrated that these compounds can increase ABCA-1 and scavenger receptor class B type 1 (SRB-1) expression in macrophages [104], two key components of reverse cholesterol transport.

Cranberry flavonoids can also induce hepatic LDL receptor expression leading to an increase in cholesterol uptake by HepG2 cells [105], therefore suggesting that cranberries could enhance the clearance of LDL particles.

As already mentioned, the circulating OxLDL level has been found to be a useful marker for identifying patients with heart disease [34–37]. Flavonoids are known to be potent antioxidants, which is a likely explanation for the lowering effect of cranberry extracts on *in vitro* LDL oxidation [105, 106]. Supportive of this effect, we have reported that a 14-day supplementation with low-calorie CJ significantly reduced by 10% the circulating concentration of OxLDL in 21 healthy men [82]. This was noted in the absence of any change in LDL particle size and number, which are strong determinants of the susceptibility of LDL particles to oxidation [107–110].

8 Anti-inflammatory action

There is accumulating evidence that quercetin, a flavonol found in large quantities in cranberries [59], is a potent down-regulator of the nuclear factor-kappa B (NF-κB) pathway [111, 112]. Numerous genes of inflammatory proteins are under the regulation of NF-κB, including adhesion molecules (ICAM-1, VCAM-1 and E-selectin), macrophage chemotactic protein-1 (MCP-1), interleukin-6 (IL-6), TNF-α and inflammatory enzymes like iNOS, cyclooxygenase-2 (COX-2) and 5-lipoxygenase (LOX) [113]. So far, no studies in humans has shown a reduction in the activation of NF-κB following CJ consumption, although we noted a significant decrease in plasma ICAM-1 and VCAM-1 following a low-calorie CJ supplementation for 12 weeks in abdominally obese men (Couillard *et al*., unpublished observations), an observation that could be attributed to inactivation of the NF-κB pathway not only by increased consumption of quercetin but also by a concomitant reduction in OxLDL particles [113]. Other components like proanthocyanidins [114], anthocyanidins [115], hydroxycinnamic acid [115] and acetylsalicylic acid [116, 117] that can be found in cranberries have all been shown to prevent expression of VCAM-1 and ICAM-1 induced by TNFα through their inhibitory action on NF-κB activation *in vitro*. Furthermore, components of the non-dialyzable material of cranberries, which include proanthocyanidins have been shown to reduce lipopolysaccharide (LPS)-induced inflammatory cytokine production such as IL-6, TNFα, CRP, IL-8 in macrophages [118], which although tested in the context of dental pathology are also relevant to the atherosclerotic process.

ApoAI, a major protein constituent of HDL particle has been reported to be anti-inflammatory [119]. An increase in apoAI has been suggested to explain the HDL-raising effect of CJ [96]. Elevation in circulating apoAI would also increase the anti-inflammatory potential to HDL particles.

Recently, resveratrol supplementation has been reported to improve the health and survival of mice fed a high-calorie diet [120]. Although the study mainly focused on survival, motor function and insulin sensitivity, the beneficial impact of resveratrol, a polyphenolic compound present in cranberries, on cardiovascular health through anti-inflammatory processes cannot be excluded. Indeed, resveratrol has been shown to suppress the expression of inflammatory genes relevant to CVD through the activation of the NF-κB [121, 122] and JAK/STAT3 [123] pathways in cultured cells.

9 Modulation of plaque stability and thrombosis

Inflammation can be a trigger for the expression of Matrix metalloproteinases (MMP), which are endopeptidases involved in the homeostasis of the extracellular matrix (ECM). In this regard, they play a role in the development of hypertension and strongly influence atherosclerotic plaque stability [124, 125]. Extracts from various fruits (raspberries, blackberries, blueberries and muscadine grapes) have been shown to inhibit MMP-2 and MMP-9 expression *in vitro* [126, 127]. To that effect, proanthocyanidins [127] as well as the flavonol myricetin [128] were identified to have the most effective inhibitory activity. Furthermore, resveratrol has also been shown to reduce MMP-9 expression through inhibition of the NF-κB [129] as well as c-Jun N-terminal kinase (JNK) and protein kinase C (PKC)-δ [130] pathways. As these polyphenolic compounds are found in cranberries, consumption of these fruits or their related products could be found to be a way to modulate MMP expression. Preliminary results from our group have shown a 30% decrease in plasma MMP-9 concentrations following a 12-wk supplementation study in men with abdominal obesity (Couillard *et al*., unpublished observations).

Cranberry is known to contain salicylic acid, the active form of acetylsalicylic acid (*i.e*. aspirin) [84]. Primary intervention study with aspirin are consistent on its beneficial impact with regards to CVD risk [131]. Part of those benefits have been suggested to come from inhibition of platelet activation and aggregation as well as its anti-inflammatory action. Some recent evidences have shown an increase in plasma salicylate concentrations after consumption of 750 mL/day of CJ for 2 weeks, suggesting bioavailability of CJ salicylates [84]. This fact has also raised the question as to whether or not CJ could decrease platelet aggregation *in vivo*. However, no study has yet demonstrated the effects of consuming CJ on platelet aggregation in humans and linked this effect to salicylates. On the other hand, animal [132] and human [133] studies found that grape juice has a beneficial impact on platelet aggregation. Interestingly, flavonols, anthocyanidins and proanthocyanidins are the flavonoids most common in grapes and cranberries and the potential antithrombotic of the latter can only be suggested until proven or refuted.

Finally, cranberry water extract has been shown to inhibit angiotensin converting enzyme (ACE) activity [134], which could be associated to a hypotensive effect of cranberries and another way through which cranberries could exert their cardioprotective potential.

10 Conclusion

In summary, the information available in the literature is increasingly supportive of the cardioprotective potential of cranberries. These benefits include improvements in plasma lipids and vascular function as well as reduction of the systemic and vascular inflammatory response. Furthermore, more clinical studies are clearly needed to ascertain the observations that have been published so far using more fundamental approaches. We must emphasize that CJ is not

the only key to cardiovascular health and longevity but may be an eloquent example showing that through simple and sustainable dietary modifications, *e.g.* eating more fruits and vegetables, one could significantly obtain metabolic improvements. Further studies will also guide us in knowing if phenolic enrichment of foods and fruits like cranberries will yield greater benefits on CVD risk and help us live a long and fruitful life.

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