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The impact of cranberry (*Vaccinium macrocarpon*) and cranberry products on each component of the metabolic syndrome: a review

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Abstract

Background: Some studies have shown that cranberry (*Vaccinium macrocarpon*) has beneficial effects on the components of the metabolic syndrome (MetS), a condition characterized by a cluster of cardiovascular risk factors such as central obesity, hypertension, impaired glucose homeostasis, elevated triglycerides, and decreased HDL cholesterol levels. Cranberry is very rich in polyphenols, which may significantly reduce cardiovascular disease (CVD) risk.

Main body of the abstract: Nutritional intervention studies have indicated that the intake of cranberries and cranberry products may have the following impact on metabolic health: (1) attenuate markers of obesity such as body weight, body mass index, and waist circumference; (2) reduce systolic and diastolic pressures; (3) decrease plasma concentrations of triglycerides and oxidized LDL-cholesterol, as well as increase HDL cholesterol; and (4) promote glucose homeostasis. In addition, nutritional intervention with cranberries could confer antioxidant and anti-inflammatory properties and the ability to reduce biomarkers of atherosclerosis associated with the MetS, such as homocysteine.

Short conclusion: Although there has been promising results, particularly related to lipid profile and blood pressure, further research is needed to support the recommendation of cranberry intake as a nutritional intervention for the treatment of MetS.

Keywords: Cranberry, Inflammation, Bioactive compounds, Polyphenols, Metabolic syndrome

Background

Metabolic syndrome (MetS) is generally defined as a complex disorder represented by a cluster of cardiovascular risk factors such as central obesity, dyslipidemia, hypertension, and impaired glucose metabolism, leading to an increased risk of coronary heart diseases, other types of atherosclerotic cardiovascular diseases, and type 2 diabetes (DT2) [1]. Recent evidence suggests that the prevalence of MetS is increasing in both developed and developing countries, such as Brazil [2, 3].

Diets rich in fruits and vegetables, especially those considered berries, increase the intake of polyphenols, which are known to confer benefits to the cardiovascular health [4, 5]. Cranberries (*Vaccinium macrocarpon*) are native fruits from North America that contain low carbohydrate concentrations in comparison to other fruits. Furthermore, they have high content of vitamins, minerals, and polyphenolic compounds [6], such as flavan-3-ols, anthocyanins, benzoic acid, and ursolic acid [7]. A-type proanthocyanidins are also present in high concentrations in cranberry, while other berries predominantly have B-type proanthocyanidins. B-type proanthocyanidins are believed to be less bioavailable than the A-type [8]. The most abundant flavonoids in cranberries consist mainly of quercetin and myricitrin [7].

Moreover, it has been demonstrated that cranberry juice may contain resveratrol in concentrations similar to grape juice [9]. Resveratrol has several biological effects related to cardiovascular health, including inhibition of platelet aggregation and reduction of inflammation [6]. The

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polyphenols present in cranberry have a wide variety of biological effects, including antibacterial, anticarcinogenic, antiangiogenic, anti-inflammatory, antioxidant, modulating enzyme activity, and gene expression regulation [7, 10–16].

Cranberry juice may contain 100% of the daily requirement of vitamin C, contributing to the beneficial effects of the fruit [10]. Cranberries can be consumed in various products such as industrialized juice, jam, frozen fruit pulp, sauce, cereal bars, and capsules and have become increasingly popular and consumed, after several researches have indicated health benefits including possibly preventing diseases such as urinary tract infection [17].

According to observational and interventional studies in humans, consumption of cranberry and cranberry products may be associated with beneficial effects on MetS, affecting one or more of its components [6, 18], a variety of inflammatory biomarkers and oxidative stress [19]. Thus, the present review gathers recent and relevant literature involving the consumption of cranberry products and the components of the MetS in humans, in addition to highlighting the most relevant mechanisms involved.

Main text

Cranberry and obesity

Obesity has become a major public health issue, and it is growing worldwide. In 2012, approximately 34.9% of American adults were classified as obese [20]. Obesity is usually defined when body mass index (BMI) is greater than or equal to 30 kg/m^2. Abdominal obesity is defined as a waist circumference (WC) above 102 cm in men and 88 cm in women [21]. Additionally, other waist circumference values have been applied for the diagnosis of abdominal obesity in MetS to improve their applicability to different ethnic groups [21, 22]. Some recommended waist circumference thresholds are as follows: for Europeans and South Americans (≥94 cm in men and ≥80 cm in women), South Asians and Chinese (≥90 cm in men and ≥80 cm in women), Japanese (≥85 cm in men and ≥90 cm in women), and Americans and Canadians (≥102 cm in men and ≥88 cm in women) [21, 22].

An epidemiological study with data from the National Health and Nutrition Examination Survey (NHANES) including 10,891 American adults showed that cranberry juice consumers were more likely to have normal weight and lower waist circumference. The authors attributed the favorable effects on body composition to flavonoids, which are present in high levels in cranberries [23]. Other studies have demonstrated that bioactive compounds such as flavonoids have the potential to inhibit lipogenesis and adipogenesis, stimulate lipolysis, and induce apoptosis in adipocytes [24]. It has been previously demonstrated that cranberry reduces the proliferation and viability of 3T3-L1 pre-adipocytes in a dose-dependent manner. The nutritional intervention with this berry also reduced the number of adipocytes and reduced the accumulation of lipids in the 3T3-L1 pre-adipocytes, indicating an inhibitory effect on lipogenesis. Furthermore, it was demonstrated that cranberry induced lipolysis in adipocytes and reduced the expression of PPARγ, C/EBPb, and SREBP1, which are important transcription factors of the adipogenesis pathway [25].

Diet is closely related to the development of obesity; therefore, a diet enriched with these compounds may serve as an additional strategy for the prevention and treatment of obesity. The main human-interventional studies with cranberry or cranberry products considering markers of obesity are listed in Table 1. In sum, although an epidemiological study [23] verified that consumers of cranberry drinks were more likely to have more favorable anthropometric measures, clinical trials on this subject are still scarce and the results are inconsistent. Therefore, more work is needed to obtain stronger evidence.

Cranberry and glucose metabolism

Glucose homeostasis is disturbed when insulin and fasting glucose are greater than 20 mU/mL and 110 mg/dL, respectively, or when the patient has to use medication to control blood glucose [26]. Matthews et al. [27] described a mathematical relationship (HOMA-IR model) between fasting glycemia and insulin to predict insulin resistance [28]. Lower HOMA-IR values represent higher insulin sensitivity, and higher values correspond to decreased insulin sensitivity, also known as insulin resistance (IR). IR and hyperinsulinemia contribute to the pathogenesis of type 2 diabetes.

Wilson et al. [29] studied postprandial insulin and glucose response in patients with type 2 diabetes. The subjects were allocated into four groups that received: a single serving of white bread (57 g, 160 calories, 1 g of fiber); raw cranberries (55 g, 21 calories, 1 g of fiber); sweetened cranberries (40 g, 138 calories, 2.1 g of fiber); or cranberries with low sugar and high fiber content (40 g, 113 calories, 1.8 g of fiber, and 10 g polydextrose). The investigators found that the consumption of low-sugar, high-fiber cranberries resulted in more favorable glucose and insulin peaks. Thus, the selection of dry cranberries, a natural source of polyphenols and fibers, would enable a more favorable glycemic response in patients with T2D. The decrease in glucose peak may be due to the presence of the soluble fibers polydextrose and β-Glucan, which were present in the low-calorie serving, since these compounds have been related to the reduction in the rate of gastric glucose absorption [30, 31]. The presence of flavonoids in cranberry juice

Table 1 Intervention studies with cranberry products evaluating markers of obesity

Authors	Studies	Population/intervention	Conclusion
Ruel et al., 2006 [12]	Intervention study to evaluate the effect of increasing daily consumption of a low-calorie cranberry juice cocktail on plasma lipid profile in abdominally obese men.	30 men consumed increasing doses of cranberry juice for three consecutive 4-week periods (125 mL, 250 mL e 500 mL/d).	There was a decrease in adiposity measures after the intervention period, with reduction of body weight ($p = 0.0263$), BMI ($p = 0.0386$) and WC ($p < 0.0001$).
Basu et al., 2011 [16]	Randomized, double-blind, placebo-controlled clinical trial to assess the effect of intake of low calorie cranberry juice on CVD risk factors such as lipid oxidation, inflammation and dyslipidemia in subjects with MetS.	31 patients with MetS consumed 480 mL of juice/day (n = 15) or placebo (n = 16) for 8 weeks.	Consumption of 480 mL of cranberry juice/day for 8 weeks showed no significant effect on WC reduction.
Duffey and Sutherland, 2013 [23]	A study to verify the association between consumption of cranberry beverage, macronutrient intake and body mass of patients who participated in the National Health and Nutrition Examination Survey (NHANES) between 2005-2008.	10891 American adults aged 19 years or older selected by the National Health and Nutrition Examination Survey (NHANES) between 2005-2008.	Consumers of cranberry drinks were more likely to have normal body weight ($p < 0.001$) and less likely to be overweight or obese (BMI ≥ 25 kg/m^2, $p < 0.001$) compared to non-consumers.
Simão et al., 2013 [6]	Clinical trial to evaluate the effect of intake of low calorie cranberry juice on metabolic and inflammatory biomarkers in MetS patients.	56 patients with MetS participated in a 60-day study; 20 patients consumed 700 mL of cranberry juice/day and 36 did not consume the juice.	The consumption of 700 mL of cranberry juice/day for 60 days showed no significant effects on the reduction of BMI or WC.

BMI body mass index, *CVD* cardiovascular disease, *WC* waist circumference, *MetS* metabolic syndrome

can also delay the intestinal absorption of glucose [32], contributing to the improvement in the glycemic response observed in previous studies carried out by the same research group [33].

In vitro studies have demonstrated that the extent of inhibition of α-glucosidase by berry extracts is related to its anthocyanin content [34]. Cyanidin-3-rutinoside [35] and cyanidin-3-galactoside [36] are considered α-glucosidase inhibitors. Proanthocyanidins are also considered potent α-glucosidase inhibitors [37]. Barrett et al. [38] conducted an in vitro study to investigate if the tannins (proanthocyanidins and elagitannins) present in pomegranate, cranberry, grape, and cocoa extracts could bind to the digestive enzymes α-amylase and glucoamylase, thus inhibiting starch hydrolysis. The authors concluded that not only were tannins capable of inhibiting these enzymes but also larger and more complex tannins such as cranberries would have the ability to inhibit enzymes more effectively than less polymerized tannins, such as those present in cocoa [38]. Another in vitro study has shown that cranberry procyanidins have the ability to inhibit the glycation of human hemoglobin and serum albumin by elimination of reactive carbonyl radicals [39].

Some phenolic acids, such as chlorogenic, ferulic, and caffeic acids, competitively inhibit glucose uptake mediated by sodium-dependent glucose transporter 1 (SGLT1) [19]. This inhibition has also been observed by other glucosides and quercetin [32]. SGLT1 assists in the intestinal absorption of glucose through the aid of sodium-dependent transport and thereby facilitates the independent transport of sodium via GLUT [9]. The flavonoids mycetin and quercetin were responsible for the inhibition of GLUT2 glucose transport [37, 40]. These compounds that inhibit glucose uptake, such as phenolic acids and flavonoids, are components present in berries [41–43]. Furthermore, it has been demonstrated in porcine models that quercetin inhibits gastric uptake of glucose. Quercetin and myricetin have also been shown to inhibit GLUT4-mediated glucose uptake in rodent adipocytes, to inhibit aldose reductase, α-amylase and α-glucosidase in vitro [44].

Although polyphenolic compounds present in berries have been associated with the enhancement of glycemic regulation, other components may contribute to these effects. Törrönen et al. [45] investigated the effects of whole-berry *purées* on the postprandial glucose and insulin responses after consumption of white wheat bread or rye bread. The berry mixture (strawberries, bilberries, cranberries, and blackcurrants) significantly reduced the postprandial insulin response after the intake of white wheat bread or rye bread. The researchers observed that although the consumption of berries did not suppress postprandial peak glucose, less insulin was required for the maintenance of postprandial glucose metabolism [45]. According to the investigators, the more desirable postprandial insulin response did not appear to be related to the polyphenol composition of

the berries, but rather the fiber content, especially soluble fiber [45].

The main human-interventional studies with cranberry or cranberry products considering glycemic metabolism are listed in Table 2. In sum, although nutritional intervention studies with cranberries on glucose metabolism are still scarce, some of them have shown that cranberry products may promote glucose homeostasis by reducing fasting glycemia, improving HOMA-IR, increasing insulin sensitivity, and preventing compensatory insulin secretion [44, 46, 47], whereas others did not demonstrate any significant change on this feature [16, 48]. From these studies, it is still not possible to define if duration and consumed amount of cranberry are responsible for these controversial results. Certainly, more work is warranted on this issue.

Cranberry and blood pressure

Polyphenols may significantly reduce cardiovascular disease (CVD) risk [49, 50]. In a study conducted during 18 years, it was demonstrated that the combined intake three times a week of berries was associated with a lower risk of myocardial infarction in middle-aged women [5]. Cranberries are rich sources of several polyphenols, such as quercetin which has been associated with significant blood pressure reduction in animal models [51–54] and human trials [51–54]. Mechanistic studies in mouse models have reported that cranberry juice induces vasodilation via endothelial nitric oxide synthase (eNOS) and significant reduction of blood pressure. These vasorelaxing properties would be comparable to those of red wine [55].

Thirty men participated in a 12-week intervention study and were asked to consume increasing daily doses of a cranberry juice cocktail (125, 250, and 500 mL/day) over three successive periods of 4 weeks. The investigators noted a slight but significant decrease in SBP (−3 mm Hg) over the course of the intervention [13]. This reduction was likely associated with the polyphenolic content of the beverage. Furthermore, nutritional studies have associated the intake of berries with cardioprotective effects [49, 56–58]. Intervention studies with flavonoids and anthocyanins have indicated that possible mechanisms for the reduction of blood pressure are inhibition of the activity of the angiotensin-converting enzyme [13], a significant increase in nitric

Table 2 Intervention studies with cranberry products evaluating markers of glucose metabolism

Authors	Studies	Population/intervention	Conclusion
Lee et al. [48]	A randomized double blind, controlled study evaluating the effect of cranberry intake on the lipid profile of patients with T2D.	30 type 2 diabetic subjects received cranberry supplements (500 mg/capsule) or placebo, 3×/day, for 12 weeks.	Neither fasting glucose nor glycated hemoglobin improved in either group.
Basu et al. [16]	Randomized, double-blind, placebo-controlled clinical trial to assess the effect of intake of low calorie cranberry juice on CVD risk factors such as lipid oxidation, inflammation and dyslipidemia in subjects with MetS.	31 patients with MetS consumed 480 mL of juice/day ($n = 15$) or placebo ($n = 16$) for 8 weeks.	Consumption of 480 mL of cranberry juice per day for 8 weeks showed no significant effect on the reduction of fasting glycemia.
Shidfar et al. [44]	A randomized, double-blind, placebo-controlled clinical trial to verify the effect of cranberry juice on PON-1, apoA-1, apoB, glucose, and Lp (a) in T2D patients.	Patients with T2D consumed 240 mL of juice/day ($n = 29$) or placebo ($n = 29$) for 12 weeks.	Patients who consumed cranberry juice had a significant decrease in serum glycemia when compared to the initial value ($P < 0.01$) and the control group ($P < 0.05$).
Novotny et al. [46]	A double blind, placebo-controlled study evaluating the consumption of low-calorie cranberry juice and placebo drink to decrease cardiometabolic risk in overweight middle-aged population.	Overweight patients consumed 240 mL of juice ($n = 29$) or placebo ($n = 27$) two times/day for 8 weeks.	Patients who consumed low-calorie cranberry juice had a reduction in fasting plasma glucose ($P = 0.03$). The juice also had a beneficial effect on HOMA-IR for participants with high baseline values ($P = 0.035$).
Paquette et al. [47]	A parallel, double-blind, controlled, and randomized clinical trial to determine the effects of strawberry and cranberry polyphenols (SCP) on insulin sensitivity, glucose tolerance, insulin secretion, lipid profile, inflammation, and oxidative stress markers in free-living insulin-resistant overweight or obese human subjects.	Overweight or obese patients consumed a SCP beverage (333 mg) ($n = 20$) or control beverage ($n = 21$) daily for 6 weeks.	Patients who consumed the polyphenols beverage had an increase in insulin sensitivity and prevention of further compensatory insulin secretion.

MetS metabolic syndrome, *PON-1* paraoxonase-1, *Lp (a)* lipoprotein (a), *T2D* type two diabetes mellitus

oxide synthesis by endothelial cells [59, 60], reduction of vasoconstriction via nitric oxide-mediated pathway, or reduction of renal oxidative stress [61, 62]. Dietary intervention with polyphenol-rich foods and berry beverages has led to significant changes in MetS characteristics, including reduction of blood pressure, abdominal adiposity, dyslipidemia, inflammation, and oxidative stress [63].

The main human-interventional studies with cranberry or cranberry products considering blood pressure are listed in Table 3, and although this is a valuable area of interest, the scarce studies have found controversial results to date and for sure more studies are needed on this subject.

Cranberry and dyslipidemia

Cardiovascular diseases are among the leading causes of death in North America [64, 65]. Although LDL cholesterol is not included in the definition of metabolic syndrome, elevated concentration of low-density lipoprotein (LDL) is one of the most important cardiovascular risk factor [66]. LDL particles, such as oxidized LDL, could at least partially explain the atherogenicity of LDL [67, 68]. Oxidized LDL is not recognized by LDL receptors, but rather by cell-surface receptors on macrophages; oxidation of LDL promotes cholesterol absorption, leading to the formation of foam cells, which is the first step in the formation of the first atherosclerotic lesions [64]. A decrease in HDL concentration is also an independent risk factor for CVD [69]. Although the role of HDL in the cholesterol transport is known, HDL has several other cardioprotective effects such as antithrombogenic, antioxidant, fibrinolytic, antiadherence, and anti-inflammatory properties [70].

The lipid-lowering effects of cranberry can be attributed mainly to the phytochemical compounds contained in the fruit and to the fiber content, depending on the form of consumption. Cranberry is a relevant source of flavonoids, such as anthocyanidins, proanthocyanidins [71, 72], resveratrol [73], and phenolic acid [71]. Flavonoids, abundantly present in cranberry, would have the ability to inhibit the oxidation of LDL-cholesterol. Oxidized LDL plays a critical role in the initiation and progression of atherosclerosis; thus, supplementation with cranberry would have the potential to delay the process of atherosclerotic CVD [74]. In addition, flavonoids would have the ability to inhibit platelet adhesion and aggregation, inhibit enzymes involved in lipid and lipoprotein metabolism, and could increase reverse cholesterol transport, lowering total and LDL cholesterol [4]. Anthocyanin-rich products reduced triglycerides in animal models [75–77]. The total dietary fiber content of cranberry may reach 5 g/100 g in dried fruit and thus may contribute to its cholesterol lowering effects [4].

The flavonoid quercetin has been shown to inhibit de novo TAG synthesis [78]. Casaschi et al. [78] analyzed the activity of diacylglycerol acyltransferase (DGAT), an enzyme in the final reaction of the glycerol phosphate pathway for TAG synthesis, and found reduced DGAT activity after treatment with quercetin. The investigators also found that quercetin inhibits microsomal TAG transfer protein (MTP) activity, an enzyme that catalyzes the transfer of lipids, such as TAG and cholesterol esters, which would inhibit intestinal apolipoprotein B secretion and total cholesterol, TG and LDL levels [78].

Table 3 Intervention studies with cranberry products evaluating blood pressure

Authors	Studies	Population/intervention	Conclusion
Ruel et al. [13]	Intervention study to determine the effect of the daily consumption of low-calorie cranberry juice cocktail on plasma oxidized LDL, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin concentrations in men.	30 men consumed increasing doses of cranberry juice for 3 consecutive 4-week periods (125, 250, and 500 mL/day).	There was a slight but significant decrease in systolic blood pressure over the course of the intervention (−3 mm Hg, $P = 0.03$).
Basu et al. [16]	Randomized, double-blind, placebo-controlled clinical trial to assess the effect of intake of low calorie cranberry juice on CVD risk factors such as lipid oxidation, inflammation, and dyslipidemia in subjects with MetS.	31 patients with MetS consumed 480 mL of juice/day ($n = 15$) or placebo ($n = 16$) for 8 weeks.	Consumption of 480 mL of cranberry juice per day for 8 weeks showed a non-significant reduction in systolic blood pressure compared to baseline values (−5.3%, $P = 0.07$).
Novotny et al. [46]	A double blind, placebo-controlled study evaluating the consumption of low-calorie cranberry juice and placebo drink to decrease cardiometabolic risk in overweight middle-aged population.	Overweight patients consumed 240 mL of cranberry juice ($n = 29$) or placebo ($n = 27$) two times/day for 8 weeks.	After 8 weeks, diastolic pressure was significantly lower in the cranberry juice group than in the placebo group ($P = 0.048$), with no difference in systolic pressure.

CVD cardiovascular disease, *MetS* metabolic syndrome

Ruel et al. [12] proposed that the HDL increase could be related to an increased production of apolipoprotein A-I or a decreased clearance of HDL particles following intervention with cranberry juice. The authors also hypothesized that a reduction in apolipoprotein A-I oxidation (related to a decrease in oxidative stress) and an increased expression of paraoxonase-1 (related to the high content of quercetin in the beverage) could be at least partially responsible for the increase in HDL. Another proposed mechanism to explain HDL increase after intervention with cranberry products and reduction in serum triglyceride (TG) levels is the inverse relationship between TG and HDL [12, 79]. In hypertriacylglycerolemic states, HDL particles exchange cholesterol for TG with LDL and very low-density lipoproteins (VLDL) and become TG-rich. The TG-rich HDL particles are more rapidly catabolized in the liver than normal HDL particles. Thus, after a decrease in serum levels of TG, an increase in serum HDL levels may occur [12, 79, 80].

The main human-interventional studies with cranberry or cranberry products considering lipid profile are listed in Table 4. Collectively, these nutritional findings suggest that although cranberry products have shown promising beneficial effects on lipid profile, this is observed only in

Table 4 Intervention studies with cranberry products evaluating lipid profile

Authors	Studies	Population/intervention	Conclusion
Ruel et al. [118]	Intervention study to evaluate the impact of cranberry juice consumption on LDL oxidation and on the antioxidant capacity of plasma.	21 healthy men, consuming cranberry juice (7 mL/kg body weight/day) for 14 days.	After 14 days, no change was observed in the levels of LDL-cholesterol and oxidized LDL.
Ruel et al. [12]	Intervention study to evaluate the effect of increasing daily consumption of a low-calorie cranberry juice cocktail on plasma lipid profile in abdominally obese men.	30 men consumed increasing doses of cranberry juice for 3 consecutive 4-week periods (125, 250, and 500 mL/day).	After 12 weeks, there was a significant increase in HDL ($P = 0.001$), reduction in TGs ($P = 0.0553$), and significant decrease in total cholesterol/HDL ratio ($P = 0.0005$).
Ruel, et al. [13]	Controlled intervention study evaluating the effect of low-calorie cranberry juice on plasma oxidized LDL, ICAM-1, and VCAM-1 in healthy subjects.	30 men consumed increasing doses of cranberry juice for 3 consecutive 4-week periods (125, 250, and 500 mL/day).	The intervention produced a decrease in the plasma concentration of oxidized LDL ($P < 0.0001$), but did not significantly affect total cholesterol levels and LDL cholesterol.
Lee et al. [48]	A randomized double blind, controlled study evaluating the effect of cranberry intake on lipid profile in patients with T2D.	30 type 2 diabetic subjects received cranberry supplements (500 mg/capsule) or placebo, 3×/day, for 12 weeks.	Supplementation with cranberry is effective in reducing the arteriosclerotic cholesterol profile, including LDL, total cholesterol, and total cholesterol/HDL ratio.
Basu et al. [16]	Randomized, double-blind, placebo-controlled clinical trial to assess the effect of intake of low calorie cranberry juice on CVD risk factors such as lipid oxidation, inflammation, and dyslipidemia in subjects with MetS.	31 patients with MetS consumed 480 mL of juice/day ($n = 15$) or placebo ($n = 16$) for 8 weeks.	The consumption of 480 mL of cranberry juice/day for 8 weeks did not show significant effects on reduction of lipid profile.
Novotny et al. [46]	A double blind, placebo-controlled study evaluating the consumption of low-calorie cranberry juice and placebo drink to decrease cardiometabolic risk in overweight middle-aged population.	Overweight patients consumed 240 mL of cranberry juice ($n = 29$) or placebo ($n = 27$) two times/day for 8 weeks.	TGs were lower for those who consumed cranberry juice compared to the placebo group ($P = 0.027$). No differences in serum total cholesterol, LDL, and HDL.
Paquette et al. [47]	A parallel, double-blind, controlled, and randomized clinical trial to determine the effects of strawberry and cranberry polyphenols (SCP) on insulin sensitivity, glucose tolerance, insulin secretion, lipid profile, inflammation, and oxidative stress markers in free-living insulin-resistant overweight or obese human subjects.	Overweight or obese patients consumed a SCP beverage (333 mg) ($n = 20$) or control beverage ($n = 21$) daily for 6 weeks.	After 6 weeks, no differences were detected between the two groups for lipids.

ICAM-1 intercellular adhesion molecule-1, *VCAM-1* vascular cell adhesion molecule-1, *TGs* triglycerides

interventions lasting at least 12 weeks. Thus, further clinical trials are needed to confirm these findings and establish the duration and dose of the intervention.

Cranberry and markers of inflammation and oxidative stress

Central obesity and insulin resistance are the main features involved in MetS, but low-grade chronic inflammation is considered a major link between the MetS and CVD [81]. In MetS, central obesity is considered an important source of low-grade chronic inflammation [82].

Free radicals and reactive metabolites, also known as reactive oxygen species (ROS), are normal products of cellular metabolism and are generated primarily by the mitochondrial respiratory chain. When there is an imbalance between the production of these reactive species and their elimination by antioxidant mechanisms, an accumulation of ROS occurs, leading to oxidative stress. Several diseases such as cancer, chronic inflammatory diseases, and aging are all conditions associated with increased oxidative stress [83–86]. Furthermore, continuous oxidative stress may lead to chronic inflammation [87].

A methanol extract prepared from dehydrated cranberries inhibited the activity of cyclooxygenase-2 and also inhibited the NF-κβ transcriptional activation in human T lymphocytes. Furthermore, the extract inhibited the release of interleukins (IL)-1β, IL-6, IL-8, and tumor necrosis factor-α from lipopolysaccharide (LPS)-stimulated human peripheral blood mononuclear cells in vitro. The authors attributed the anti-inflammatory effects to ursolic acid and ursolic acid derivatives present in the cranberry extract [88].

Vinson et al. [89] investigated the quantity of both free and total phenolic antioxidants in cranberry products

Table 5 Intervention studies with cranberry products evaluating markers of inflammation and oxidative stress

Authors	Studies	Population/intervention	Conclusion
Ruel et al. [12]	Intervention study to evaluate the effect of increasing daily consumption of a low-calorie cranberry juice cocktail on plasma lipid profile in abdominally obese men.	30 men consumed increasing doses of cranberry juice for 3 consecutive 4-week periods (125, 250, and 500 mL/day).	Reduction of nitrite/nitrate concentration ($P < 0.05$) with a significant association between plasma nitrite/nitrate decrease and apo A-1 increase ($P < 0.05$). After the 12-week period, the antioxidant capacity of total plasma increased significantly ($P = 0.006$).
Basu et al. [16]	Randomized, double-blind, placebo-controlled clinical trial to assess the effect of intake of low calorie cranberry juice on CVD risk factors such as lipid oxidation, inflammation, and dyslipidemia in subjects with MetS.	31 patients with MetS consumed 480 mL of juice/day ($n = 15$) or placebo ($n = 16$) for 8 weeks.	Cranberry juice significantly increased plasma antioxidant capacity ($P < 0.05$) and decreased oxidized LDL and malondialdehyde ($P < 0.05$) at 8 weeks versus placebo.
Simão et al. [6]	Clinical trial to evaluate the effect of low calorie cranberry juice intake on metabolic and inflammatory biomarkers in MetS patients.	56 patients with MetS participated in a 60-day study; 20 patients consumed 700 mL of cranberry juice/day, and 36 did not consume the juice.	The consumption of 700 mL of cranberry juice/day for 60 days decreased lipoperoxidation ($P = 0.036$) and protein oxidation ($P = 0.008$) and increased adiponectin levels ($P = 0.01$). The metabolic and inflammatory biomarkers C-reactive protein, TNF-α, IL-1, and IL-6 did not differ between the groups.
Novotny et al. [46]	A double blind, placebo-controlled study evaluating the consumption of low-calorie cranberry juice and placebo drink to decrease cardiometabolic risk in overweight middle-aged population.	Overweight patients consumed 240 mL of cranberry juice ($n = 29$) or placebo ($n = 27$) two times/day for 8 weeks.	After 8 weeks of evaluation, there was significant improvement in C-reactive protein levels ($P = 0.0054$) for individuals consuming the low-calorie cranberry juice than for individuals consuming the placebo beverage.
Paquette et al. [47]	A parallel, double-blind, controlled, and randomized clinical trial to determine the effects of strawberry and cranberry polyphenols (SCP) on insulin sensitivity, glucose tolerance, insulin secretion, lipid profile, inflammation, and oxidative stress markers in free-living insulin-resistant overweight or obese human subjects.	Overweight or obese patients consumed a SCP beverage (333 mg) ($n = 20$) or control beverage ($n = 21$) daily for 6 weeks.	After 6 weeks, no differences were detected between the two groups for markers of inflammation and oxidative stress.

CVD cardiovascular disease, *MetS* metabolic syndrome, *TNF* tumor necrosis factor, *IL* interleukin

and plasma antioxidant capacity after the consumption of a single 24-mL serving of cranberry juice. The authors found cranberries and cranberry products to be a significant source of antioxidants both in vitro and in vivo.

Anthocyanin-rich products reduced inflammatory factors in humans [90, 91]. Furthermore, several studies have shown that antioxidant compounds, especially polyphenols, can inhibit the oxidation of LDL, which in turn, would reduce the expression of adhesion molecules in the endothelium [92, 93]. In addition, cranberry has salicylic acid [94], which has anti-inflammatory activity and has been shown to decrease the expression of vascular cell-1 adhesion molecule in vitro [95].

In a comparative study, cranberry juice had the same amount of resveratrol as grape juice [73]. The health benefits associated to resveratrol are many, especially in promoting cardiovascular health, elimination of reactive oxygen species, inhibition of platelet aggregation, and decrease of inflammation [9].

Although cranberries are rich in known antioxidant substances, the number of human-interventional studies with this berry considering oxidative stress is unexpectedly small. The main intervention studies considering oxidative stress and markers of inflammation are shown in Table 5. Altogether, these nutritional intervention studies seem to confirm the expected antioxidant action effect of cranberry products. However, the effects on inflammatory markers are still inconsistent. Certainly, more studies are required to confirm these results and define the optimal dose and duration of treatment.

Cranberry and other markers of cardiovascular risk

The intake of fruits and vegetables is beneficial for reducing the risks of some human diseases, such as CVD and cancer. In addition to being rich in soluble and insoluble fibers, the positive health effects are attributed to elements with antioxidant properties such as vitamins E, C, and carotenoids, which have the capacity to inactivate ROS involved in the process or progression of chronic diseases [96]. The presence of anthocyanins in berries is responsible for its coloration and comprises the largest group of natural species with water soluble vegetable pigments [97–100]. Normally, the intensity

Table 6 Studies considering other cardiovascular risk markers and consumption of cranberry

Authors	Studies	Population/intervention	Conclusion
Ruel et al. [13]	Intervention study to determine the effect of the daily consumption of low-calorie cranberry juice cocktail on plasma oxidized LDL, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin concentrations in men.	30 men consumed increasing doses of cranberry juice for 3 consecutive 4-week periods (125, 250, and 500 mL/day).	There was a significant decrease in plasma intercellular adhesion molecule-1 ($P < 0.0001$) and vascular cell adhesion molecule-1 ($P < 0.05$) concentrations over the course of the intervention.
Ruel et al. [18]	Intervention study to determine the effect of consuming increasing daily doses of low-calorie cranberry juice cocktail (CJC) on plasma matrix metalloproteinase (MMP)-9 concentrations in abdominally obese men.	30 men consumed increasing doses of cranberry juice for 3 consecutive 4-week periods (125, 250, and 500 mL/day).	There was a significant decrease in plasma MMP-9 concentrations ($P < 0.0005$) over the course of the intervention.
Dohadwala et al. [15]	This study was carried out in two stages: (1) an uncontrolled pilot study to determine the acute effects of cranberry juice consumption and (2) a randomized, double blind, cross-over study to examine vascular functions before and after consumption of cranberry juice and placebo in patients with stable coronary disease.	An acute non-placebo pilot study in participants ($n = 15$) who consumed 480 mL cranberry juice and a placebo crossover study ($n = 44$) 480 mL/day for 4 weeks with 2-week washout period between placebo/cranberry drinks.	After the pilot study, there was a significant improvement in the brachial artery dilation. No effects on blood pressure, basal, or hyperemic flow were observed. In the crossover study, there was a significant decrease of arterial stiffness with consumption of the cranberry beverage.
Simão et al. [6]	Clinical trial to evaluate the effect of intake of low calorie cranberry juice on metabolic and inflammatory biomarkers in MetS patients.	56 patients with MetS participated in a 60-day study; 20 patients consumed 700 mL of cranberry juice/day, and 36 did not consume the juice.	The consumption of 700 mL of cranberry juice/day for 60 days significantly decreased homocysteine levels ($P < 0.001$).
Ruel et al. [119]	Double-blind crossover design intervention study to determine the effect of consuming daily doses of low-calorie cranberry juice cocktail (CJC) on arterial stiffness in abdominally obese men.	35 men consumed 500 mL of cranberry juice or placebo for 4 weeks.	A significant ($P = 0.019$) within group decrease in augmentation index, an index of arterial stiffness, was noted following the consumption of 500 mL CJC/day for 4 weeks.

MetS metabolic syndrome

of the color is directly proportional to its anthocyanin content and can range from 2–4 g/kg, increasing as berries ripen. The average anthocyanin consumption in the USA is 12.5–215 mg per day [101]. Studies have shown that anthocyanins have low bioavailability, are widely conjugated in the liver and the intestine, and are excreted by the kidney within 2–8 h of ingestion [102, 103]. The content of polyphenols (including anthocyanins) and some vitamins in berries may be affected by post-harvest processing techniques, such as pressing and pasteurization, and thus reduce their effects on CVD risk [104–106].

In an in vitro study, anthocyanins were shown to be effective biomarkers of heart diseases and cancer, inhibiting the release of ROS from active human granulocytes [107] and suppressing free radical-mediated lipid peroxidation and apoptosis in cultured aortic endothelial cells [108, 109]. In addition, anthocyanins, aglycones, and glycosides are effective inhibitors of oxidative-induced DNA damage in human colon cells [110] and are potent inhibitors of tumor cell growth in vitro [111, 112].

The main intervention studies considering other markers of cardiovascular risks are shown in Table 6. The findings suggest that cranberry products may significantly improve several markers of cardiovascular risk, such as adhesion molecules, homocysteine, and arterial stiffness. Nevertheless, it still remains to be determined if this changes translate into prevention of cardiovascular events.

Gut microbiota and metabolism

A large body of evidence has elegantly demonstrated that the gut microbiome regulates fat storage, lipid metabolism, insulin resistance, and overall metabolism [113–115]. A disturbance in gut microbiota, marked by an imbalance between intestinal bacteria (e.g., increase in Firmicutes and reduction in the abundance of Bacteroidetes), known as dysbiosis, has been associated with several components of MetS, such as obesity and IR, via modulation of inflammatory pathways. Thus, microbiota modulation through various nutritional interventions has been researched [80]. Recently, it has been demonstrated that polyphenolic compounds from various berries may possess prebiotic activity [116]. Additionally, Anhê et al. [117] recently demonstrated that oral administration of a cranberry extract prevented several detrimental features of the MetS in a mouse model. The authors associated these metabolic improvements with a remarkable increase in the abundance of the mucin-degrading bacterium *Akkermansia* in the gut microbiota of mice [117]. Thus, although we are not aware to date of any human intervention study with cranberries investigating gut microbiota, this prebiotic effect may also be at least partially responsible for the beneficial health effects demonstrated.

Conclusions

Although several studies have shown beneficial effects, there are still few clinical and epidemiological studies evaluating the relationship between cranberry intake and the various components directly or indirectly associated with the MetS. In addition, most clinical studies are of relatively short duration (8 to 12 weeks), which often prevents the verification of additional beneficial effects. Another factor to consider is the amount of product to be ingested. The antioxidant action of cranberry is already well known and some authors have suggested the conduction of clinical trials to verify anti-inflammatory activity. The mechanisms of action associated to cranberry also require further studies. Although results especially related to lipid profile and blood pressure are promising, further research is needed to support the recommendation of cranberry intake as a nutritional intervention for the treatment of metabolic syndrome.

Abbreviations

BMI: Body mass index; BP: Blood pressure; CRP: C-reactive protein; CVD: Cardiovascular disease; FFAs: Free fatty acids; HDL: High-density lipoprotein; HOMA: Homeostatic model assessment; ICAM-1: Intercellular adhesion molecule-1; IL: Interleukin; IR: Insulin resistance; LDL: Low-density lipoprotein; MetS: Metabolic syndrome; Ox-LDL: Oxidized LDL; PAI-1: Plasminogen activator inhibitor-1; ROS: Reactive oxygen species; SBP: Systolic blood pressure; T2D: Type 2 diabetes; TG: Triglycerides; VCAM-1: Vascular cell adhesion molecule-1; WC: Waist circumference

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The authors declare that they have no competing interests.

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References

1. Reaven GM. Banting Lecture 1988. Role of insulin resistance in human disease. 1988. Nutrition. 1997;13:65. discussion 64, 66.
2. Ford E, Giles W, Mokdad A. Increasing prevalence of the metabolic syndrome among U.S. adults. Diabetes Care. 2004;27:2444–9.
3. Grundy S. Metabolic syndrome pandemic. Arter Thromb Vasc Biol. 2008;28: 629–36.
4. Reed J. Cranberry flavonoids, atherosclerosis and cardiovascular health. Crit Rev Food Sci Nutr. 2002;42:301–16.
5. Cassidy A, Mukamal KJ, Liu L, Franz M, Eliassen AH, Rimm EB. High anthocyanin intake is associated with a reduced risk of myocardial infarction in young and middle-aged women. Circulation. 2013;127:188–96.
6. Simão TNC, Lozovoy MAB, Simão ANC, Oliveira SR, Venturini D, Morimoto HK, et al. Reduced-energy cranberry juice increases folic acid and adiponectin and reduces homocysteine and oxidative stress in patients with the metabolic syndrome. Br J Nutr. 2013;110:1885–94.
7. Blumberg JB, Camesano TA, Cassidy A, Kris-etherton P, Howell A, Manach C, et al. Cranberries and their bioactive constituents in human health. Adv Nutr. 2013;4:618–32.
8. Appeldoorn MM, Vincken JP, Aura AM, Hollman PCH, Gruppen H. Procyanidin dimers are metabolized by human microbiota with 2-(3,4-dihydroxyphenyl) acetic acid and 5-(3,4-dihydroxyphenyl)-gamma-valerolactone as the major metabolites. J Agric Food Chem. 2009;57:1084–92.
9. Ruel G, Couillard C. Evidences of the cardioprotective potential of fruits: the case of cranberries. Mol Nutr Food Res. 2007;51:692–701.
10. McKay DL, Blumberg JB. Cranberries (Vaccinium macrocarpon) and cardiovascular disease risk factors. Nutr Rev. 2007;65:490–502.
11. Kim MJ, Jung HN, Kim KN, Kwak H-K. Effects of cranberry powder on serum lipid profiles and biomarkers of oxidative stress in rats fed an atherogenic diet. Nutr Res Pract. 2008;2:158–64.
12. Ruel G, Pomerleau S, Couture P, Lemieux S, Lamarche B, Couillard C. Favourable impact of low-calorie cranberry juice consumption on plasma HDL-cholesterol concentrations in men. Br J Nutr. 2006;96:357–64.
13. Ruel G, Pomerleau S, Couture P, Lemieux S, Lamarche B, Couillard C. Low-calorie cranberry juice supplementation reduces plasma oxidized LDL and cell adhesion molecule concentrations in men. Br J Nutr. 2008;99:352–9.
14. Wing DA, Rumney PJ, Preslicka CW, Chung JH. Daily cranberry juice for the prevention of asymptomatic bacteriuria in pregnancy: a randomized. Controlled pilot study. J Urol. 2008;180:1367–72.
15. Dohadwala MM, Holbrook M, Hamburg NM, Shenouda SM, Chung WB, Titas M, et al. Effects of cranberry juice consumption on vascular function in patients with coronary artery disease 1 – 3. Am J Clin Nutr. 2011;934–40.
16. Basu A, Betts NM, Ortiz J, Simmons B, Wu M, Lyons TJ. Low-energy cranberry juice decreases lipid oxidation and increases plasma antioxidant capacity in women with metabolic syndrome. Nutr Res. 2011;31:190–6.
17. Kontiokari T, Sundqvist K, Nuutinen M, Pokka T, Koskela M, Uhari M. Randomised trial of cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women. BMJ. 2001;322:1571.
18. Ruel G, Pomerleau S, Couture P, Lemieux S, Lamarche B, Couillard C. Plasma matrix metalloproteinase (MMP)-9 levels are reduced following low-calorie cranberry juice supplementation in men. J Am Coll Nutr. 2009;28:694–701.
19. Blumberg JB, Basu A, Krueger CG, Lila MA, Neto CC, Novotny JA, et al. Impact of cranberries on gut microbiota and cardiometabolic health: Proceedings of the Cranberry Health Research Conference 2015. Adv Nutr An Int Rev J. 2016;7:759S–70S.
20. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. JAMA. 2014;311:806–14.
21. Lean ME, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. BMJ. 1995;311:158–61.
22. Alberti KGM, Zimmet P, Shaw J, Eckel R, Grundy S, Zimmet P, et al. The metabolic syndrome—a new worldwide definition. Lancet. 2005;366:1059–62.
23. Duffey KJ, Sutherland LA. Adult cranberry beverage consumers have healthier macronutrient intakes and measures of body composition compared to non-consumers: National health and nutrition examination survey (NHANES) 2005–2008. Nutrients. 2013;5:4938–49.
24. Kowalska K. Naturalne związki zaangażowane w kontrolę masy tkanki tłuszczowej w badaniach in vitro * Natural compounds involved in adipose tissue mass control in in vitro studies. Postep Hig Med Dosw. 2011;65:515–23.
25. Kowalska K, Olejnik A, Rychlik J, Grajek W. Cranberries (Oxycoccus quadripetalus) inhibit adipogenesis and lipogenesis in 3T3-L1 cells. Food Chem. 2014;148:246–52.
26. National Cholesterol Education Program (NCEP) Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation. 2002;106:3143–421.
27. Reaven GM. Role of insulin resistance in human disease. Diabetes. 1988;37: 1595–607.
28. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412–9.
29. Wilson T, Luebke J, Morcomb E, Carrell E, Leveranz M, Kobs L, et al. Glycemic responses to sweetened dried and raw cranberries in humans with type 2 diabetes. J Food Sci. 2010;75:H218–23.
30. Xavier F. The role of viscous soluble fiber in the metabolic control of diabetes. Diabetes Care. 1997;20:1774.
31. Casiraghi MC, Garsetti M, Testolin G, Brighenti F. Post-prandial responses to cereal products enriched with barley beta-glucan. J Am Coll Nutr. 2006;25: 313–20.
32. Cermak R, Landgraf S, Wolffram S. Quercetin glucosides inhibit glucose uptake into brush-border-membrane vesicles of porcine jejunum. Br J Nutr. 2004;91:849–55.
33. Wilson T, Meyers SL, Singh AP, Limburg PJ, Vorsa N. Favorable glycemic response of type 2 diabetics to low-calorie cranberry juice. J Food Sci. 2008; 73:H241–5.
34. McDougall GJ, Shpiro F, Dobson P, Smith P, Blake A, Stewart D. Different polyphenolic components of soft fruits inhibit alpha-amylase and alpha-glucosidase. J Agric Food Chem. 2005;53:2760–6.
35. Adisakwattan S, Ngamrojanavanich N, Kalampakorn K, Tiravanit W, Roengsumran S, Yibchok-Anun S. Inhibitory activity of cyanidin-3-rutinoside on alpha-glucosidase. Enzyme. 2004;19:313–6.
36. Adisakwattana S, Charoenlertkul P, Yibchok-Anun S. α-Glucosidase inhibitory activity of cyanidin-3-galactoside and synergistic effect with acarbose. J Enzym Inhib Med Chem. 2009;24:65–9.
37. Schäfer A, Högger P. Oligomeric procyanidins of French maritime pine bark extract (Pycnogenol) effectively inhibit α-glucosidase. Diabetes Res Clin Pract. 2007;77:41–6.
38. Barrett A, Ndou T, Hughey CA, Straut C, Howell A, Dai Z, et al. Inhibition of α-amylase and glucoamylase by tannins extracted from cocoa, pomegranates, cranberries, and grapes. J Agric Food Chem. 2013;61:1477–86.
39. Liu H, Liu H, Wang W, Khoo C, Taylor J, Gu L. Cranberry phytochemicals inhibit glycation of human hemoglobin and serum albumin by scavenging reactive carbonyls. Food Funct. 2011;2:475–82.
40. Johnston K, Sharp P, Clifford M, Morgan L. Dietary polyphenols decrease glucose uptake by human intestinal Caco-2 cells. FEBS Lett. 2005;579:1653–7.
41. Määttä-Riihinen KR, Kamal-Eldin A, Mattila PH, Gonzalez-Paramas AM, Törrönen R. Distribution and contents of phenolic compounds in eighteen scandinavian berry species. J Agric Food Chem. 2004;52:4477–86.
42. Määttä-Riihinen KR, Kamal-Eldin A, Törrönen AR. Identification and quantification of phenolic compounds in berries of Fragaria and Rubus species (family rosaceae). J Agric Food Chem. 2004;52:6178–87.
43. Mattila P, Hellström J, Törrönen R. Phenolic acids in berries, fruits, and beverages. J Agric Food Chem. 2006;54:7193–9.
44. Shidfar F, Heydari I, Hajimiresmaiel SJ, Hosseini S, Shidfar S, Amiri F. The effects of cranberry juice on serum glucose, apoB, apoA-I, Lp(a), and paraoxonase-1 activity in type 2 diabetic male patients. J Res Med Sci. 2012;17:355–60.
45. Torronen R, Kolehmainen M, Sarkkinen E, Poutanen K, Mykka H, Niskanen L. Berries reduce postprandial insulin responses to wheat and rye breads in healthy women 1–4. J Nutr. 2013;143:430–6.
46. Novotny JA, Baer DJ, Khoo C, Gebauer SK, Charron CS. Cranberry juice consumption lowers markers of cardiometabolic risk, including blood pressure and circulating C-reactive protein, triglyceride, and glucose concentrations in adults. J Nutr. 2015;145:1185–93.
47. Paquette M, Medina Larqué AS, Weisnagel SJ, Desjardins Y, Marois J, Pilon G, et al. Strawberry and cranberry polyphenols improve insulin sensitivity in insulin-resistant, non-diabetic adults: a parallel, double-blind, controlled and randomised clinical trial. Br J Nutr. 2017;117:519–31.

48. Lee IT, Chan YC, Lin CW, Lee WJ, Sheu WHH. Effect of cranberry extracts on lipid profiles in subjects with type 2 diabetes. Diabet Med. 2008;25:1473–7.
49. Mink PJ, Scrafford CG, Barraj LM, Harnack L, Hong C, Nettleton JA, et al. Flavonoid intake and cardiovascular disease mortality : a prospective study in postmenopausal women 1–4. Am J Clin Nutr. 2007;86:895–909.
50. Hertog MGL, Kromhout D, Aravanis C, Ratko Buzina M, Flaminio Fidanza MD, Simona Giampaoli MD, Annemarie Jansen RD, Alessandro Menotti M, Nedeljkovic S, et al. Flavonoid intake and long-term risk of coronary heart disease and cancer in the seven countries study. Arch Intern Med. 1995;155:381–6.
51. Monteiro MMO, França-Silva MS, Alves NFB, Porpino SKP, Braga VA. Quercetin improves baroreflex sensitivity in spontaneously hypertensive rats. Molecules. 2012;17:12997–3008.
52. Ciocoiu M, Badescu L, Miron A, Badescu M. The involvement of a polyphenol-rich extract of black chokeberry in oxidative stress on experimental arterial hypertension. Evidence-based Complement Altern Med. 2013;2013.
53. Mackraj I, Govender T, Ramesar S. The antihypertensive effects of quercetin in a salt-sensitive model of hypertension. J Cardiovasc Pharmacol. 2008;51:239–45.
54. Perez-Vizcaino F, Duarte J, Jimenez R, Santos-Buelga C, Osuna A. Antihypertensive effects of the flavonoid quercetin. [Review] [48 refs]1226. Pharmacol Reports PR. 2009;61:67–75.
55. Maher MA, Mataczynski H, Stefaniak HM, Wilson T. Cranberry juice induces nitric oxide-dependent vasodilation in vitro and its infusion transiently reduces blood pressure in anesthetized rats. J Med Food. 2000;3:141–7.
56. Kuriyama S, Shimazu T, Ohmori K, Kikuchi N, Nakaya N, Nishino Y, et al. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. JAMA. 2006;296:1255–65.
57. Liu L, Nettleton J a, Bertoni AG, Bluemke D a, Szklo M. Dietary pattern, the metabolic syndrome, and left ventricular mass and systolic function: the Multi-Ethnic Study of Atherosclerosis. Am J Clin Nutr. 2009;90:362–8.
58. Janszky I, Mukamal KJ, Ljung R, Ahnve S, Ahlbom A, Hallqvist J. Chocolate consumption and mortality following a first acute myocardial infarction: the Stockholm Heart Epidemiology Program. J Intern Med. 2009;266:248–57.
59. Lazzè MC, Pizzala R, Perucca P, Cazzalini O, Savio M, Forti L, et al. Anthocyanidins decrease endothelin-1 production and increase endothelial nitric oxide synthase in human endothelial cells. Mol Nutr Food Res. 2006;50:44–51.
60. Xu JW, Ikeda K, Yamori Y. Upregulation of endothelial nitric oxide synthase by cyanidin-3-glucoside, a typical anthocyanin pigment. Hypertension. 2004; 44:217–22.
61. Kalea AZ, Clark K, Schuschke DA, Klimis-Zacas DJ. Vascular reactivity is affected by dietary consumption of wild blueberries in the Sprague-Dawley rat. J Med Food. 2009;12:21–8.
62. Shaughnessy KS, Boswall IA, Scanlan AP, Gottschall-Pass KT, Sweeney MI. Diets containing blueberry extract lower blood pressure in spontaneously hypertensive stroke-prone rats. Nutr Res. 2009;29:130–8.
63. Erlund I, Koli R, Alfthan G, Marniemi J, Puukka P, Mustonen P, et al. Favorable effects of berry consumption on platelet function, blood. Am J Clin Nutr. 2008;87:323–31.
64. Leiro J, Arranz JA, Fraiz N, Sanmartı ML. Effect of cis-resveratrol on genes involved in nuclear factor kappa B signaling. Int Immunopharmacol. 2005;5:393–406.
65. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. Heart disease and stroke statistics—2008 update A Report From the American Heart Association Statistics Committee and. 2015
66. Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med. 1999;340: 115–26.
67. Robbesyn F, Salvayre R, Negre-salvayre A. Dual role of oxidized LDL on the NF-kappaB signaling pathway. Free Radic Res. 2004;38:541–51.
68. Klouche M, May AE, Hemmes M, Meßner M, Kanse SM, Preissner KT, et al. Enzymatically modified, nonoxidized LDL induces selective adhesion and transmigration of monocytes and T-lymphocytes through human endothelial cell monolayers. Arter Thromb Vasc Biol. 1999;19:784–93.
69. Brewer Junior H. Focus on high-density lipoproteins in reducing cardiovascular risk. Am Hear J. 2004;148:S14–8.
70. Barter P, Kastelein J, Nunn A, Hobbs R, Forum F. High density lipoproteins (HDLs) and atherosclerosis; the unanswered questions. Atherosclerosis. 2003; 168:195–211.
71. Chen H, Zuo Y, Deng Y. Separation and determination of flavonoids and other phenolic compounds in cranberry juice by high-performance liquid chromatography. J Chromatogr A. 2001;913:387–95.
72. Wang PL, Du CT, Francis FJ. Isolation and characterization of polyphenolic in cranberries. J Food Sci. 1978;43:1402–4.
73. Wang Y, Catana F, Yang Y, Roderick R, Van Breemen RB. An LC-MS method for analyzing total resveratrol in grape juice, cranberry juice, and in wine. J Agric Food Chem. 2002;50:431–5.
74. Nickel T, Schmauss D, Hanssen H, Sicic Z, Krebs B, Jankl S, et al. oxLDL uptake by dendritic cells induces upregulation of scavenger-receptors, maturation and differentiation. Atherosclerosis. 2009;205:442–50.
75. Peng C, Liu L, Chuang C, Chyau C, Huang C, Wang C. Mulberry water extracts possess an anti-obesity effect and ability to inhibit hepatic lipogenesis and promote lipolysis. J Agric Food Chem. 2011;59:2663–71.
76. Prior RL, Wu X, Gu L, Hager T, Hager A, Wilkes S, et al. Purified berry anthocyanins but not whole berries normalize lipid parameters in mice fed an obesogenic high fat diet. Mol Nutr Food Res. 2009;53:1406–18.
77. Xia X, Ling W, Ma J, Xia M, Hou M, Wang Q, et al. An anthocyanin-rich extract from black rice enhances atherosclerotic plaque stabilization in apolipoprotein E–deficient mice 1. J Nutr. 2006;136:2220–5.
78. Casaschi A, Wang Q, Dang K, Richards A, Theriault A. Intestinal apolipoprotein B secretion is inhibited by the flavonoid quercetin: potential role of microsomal triglyceride transfer protein and diacylglycerol acyltransferase. Lipids. 2002;37:647–52.
79. Austin MA. Plasma triglyceride and coronary heart disease. Arterioscler Thromb. 1991;11:2–14.
80. Scavuzzi BM, Miglioranza LHDS, Henrique FC, Pitelli Paroschi T, Lozovoy MAB, Simão ANC, et al. The role of probiotics on each component of the metabolic syndrome and other cardiovascular risks. Expert Opin Ther Targets [Internet]. 2015;19:1127–38. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25872805.
81. Festa A, D'Agostino R, Jr Howard G, Mykkanen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circ J Am Hear Assoc. 2000;102:42–7.
82. Santos A-C, Lopes C, Guimarães JT, Barros H. Central obesity as a major determinant of increased high-sensitivity C-reactive protein in metabolic syndrome. Int J Obes (Lond). 2005;29:1452–6.
83. Lopez-Miranda J, Ordovas JM, Ostos MA, Marin C, Jansen S, Salas J, et al. Dietary fat clearance in normal subjects is modulated by genetic variation at the apolipoprotein B gene locus. Arterioscler Thromb Vasc Biol. 1997;17: 1765–73.
84. McCarty MF. Nitric oxide deficiency, leukocyte activation, and resultant ischemia are crucial to the pathogenesis of diabetic retinopathy/ neuropathy—preventive potential of antioxidants, essential fatty acids, chromium, ginkgolides, and pentoxifylline. Med Hypotheses. 1998;50:435–49.
85. Tsopanakis C, Tsopanakis A. Stress hormonal factors, fatigue, and antioxidant responses to prolonged speed driving. Pharmacol Biochem Behav. 1998;60:747–51.
86. Halliwell B, Gutteridge JM. Free radicals in biology and medicine. Fourth. Oxford University Press; 2006
87. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked? Free Radic Biol Med. 2010; 49:1603–16.
88. Huang Y, Nikolic D, Pendland S, Doyle BJ, Locklear TD, Mahady GB. Effects of cranberry extracts and ursolic acid derivatives on P-fimbriated Escherichia coli, COX-2 activity, pro-inflammatory cytokine release and the NF-κβ transcriptional response in vitro. Pharm Biol. 2009;47:18–25. Available from: http://www.tandfonline.com/doi/full/10.1080/13880200802397996.
89. Vinson JA, Bose P, Proch J, Al Kharrat H, Samman N. Cranberries and cranberry products: powerful in vitro, ex vivo, and in vivo sources of antioxidants. J Agric Food Chem. 2008;56:5884–91.
90. Curtis PJ, Kroon PA, Hollands WJ, Walls R, Jenkins G, Kay CD, et al. Cardiovascular disease risk biomarkers and liver and kidney function are not altered in postmenopausal women after ingesting an elderberry extract rich in anthocyanins for 12 weeks. J Nutr. 2009;139:2266–71.
91. Karlsen A, Retterstøl L, Laake P, Paur I, Kjølsrud-bøhn S, Sandvik L, et al. Anthocyanins inhibit nuclear factor-k B activation in monocytes and reduce plasma concentrations of pro-inflammatory mediators in healthy adults 1–3. J Nutr. 2007;137:1951–4.
92. Couillard C, Ruel G, Archer WR, Pomerleau S, Bergeron J, Couture P, et al. Circulating levels of oxidative stress markers and endothelial adhesion molecules in men with abdominal obesity. J Clin Endocrinol Metab. 2005;90:6454–9.

93. Kume N, Cybulsky M, Gimbrone MA. Lysophosphatidylcholine, a component of atherogenic lipoproteins, induces mononuclear leukocyte adhesion molecules in cultured human and rabbit arterial endothelial cells. J Clin Invest. 1992;90:1138–44.
94. Duthie G, Kyle J, Jenkinson A, Duthie S, Baxter G, Paterson J. Increased salicylate concentrations in urine of human volunteers after consumption of cranberry juice. J Agric Food Chem. 2005;53:2897–900.
95. Eisele G, Schwedhelm E, Schieffer B, Tsikas D, Böger R. Acetylsalicylic acid inhibits monocyte adhesion to endothelial cells by an antioxidative mechanism. J Cardiovasc Pharmacol. 2004;43:514–21.
96. Halliwell B. Effect of diet on cancer development: is oxidative DNA damage a biomarker? Free Radic Biol Med. 2002;32:968–74.
97. Wojdyło A, Oszmiański J, Bober I. The effect of addition of chokeberry, flowering quince fruits and rhubarb juice to strawberry jams on their polyphenol content, antioxidant activity and colour. Eur Food Res Technol. 2008;227:1043–51.
98. Veberic R, Jakopic J, Stampar F, Schmitzer V. European elderberry (Sambucus nigra L.) rich in sugars, organic acids, anthocyanins and selected polyphenols. Food Chem. 2009;114:511–5.
99. Hollands W, Brett GM, Radreau P, Saha S, Teucher B, Bennett RN, et al. Processing blackcurrants dramatically reduces the content and does not enhance the urinary yield of anthocyanins in human subjects. Food Chem. 2008;108:869–78.
100. Wu X, Beecher GR, Holden JM, Haytowitz DB, Gebhardt SE, Prior RL. Concentrations of anthocyanins in common foods in the United States and estimation of normal consumption. J Agric Food Chem. 2006;54:4069–75.
101. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr. 2004;79:727–47.
102. Kroon PA, Clifford MN, Crozier A, Day AJ, Donovan JL, Manach C, et al. How should we assess the effects of exposure to dietary polyphenols in vitro? Am J Clin Nutr. 2004;80:15–21.
103. Netzel M, Strass G, Kaul C, Bitsch I, Dietrich H, Bitsch R. In vivo antioxidative capacity of a composite berry juice. Food Res Int. 2002;35:213–6.
104. Wojdyło A, Figiel A, Oszmiański J. Effect of drying methods with the application of vacuum microwaves on the bioactive compounds, color, and antioxidant activity of strawberry fruits. J Agric Food Chem. 2009;57:1337–43.
105. Srivastava A, Akoh CC, Yi W, Fischer J, Krewer G. Effect of storage conditions on the biological activity of phenolic compounds of blueberry extract packed in glass bottles. J Agric Food Chem. 2007;55:2705–13.
106. Hartmann A, Patz C-D, Andlauer W, Dietrich H, Ludwig M. Influence of processing on quality parameters of strawberries. J Agric Food Chem. 2008; 56:9484–9.
107. Ggsiorowskia K, Szyba K, Brokosa B, Kolaczyliska B, Jankowiak-wlodarczyk M, Oszmiafiski J. Antimutagenic activity of anthocyanins isolated from Aronia melanocarpa fruits. 1997;119:37–46.
108. Youdim K, Martin A, Joseph J. Incorporation of the elderberry anthocyanins by endothelial cells increases protection against oxidative stress. Free Radic Biol Med. 2000;29:51–60.
109. Youdim KA, Mcdonald J, Kalt W, Joseph JA. Potential role of dietary flavonoids in reducing microvascular endothelium vulnerability to oxidative and inflammatory insults. J Nutr Biochem. 2002;13:282–8.
110. Duthie SJ, Gardner PT, Morrice PC, Wood SG, Bestwick CC, Duthie GG. DNA stability and lipid peroxidation in vitamin E-deficient rats in vivo and colon cells in vitro—modulation by the dietary anthocyanin, cyanidin-3-glycoside. Eur J Nutr. 2005;44:195–203.
111. Kamei H, Koide T, Kojimam T, Hasegawa M, Terabe K, Umeda T, et al. Flavonoid-mediated tumor growth suppression demonstrated by in vivo study. Cancer Biother Radiopharm. 2009;11:193–6.
112. Hakimuddin F, Paliyath G, Meckling K. Selective cytotoxicity of a red grape wine flavonoid fraction against MCF-7 cells. Breast Cancer Res Treat. 2004;85:65–79.
113. Backhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, et al. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci U S A. 2004;101:15718–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15505215.
114. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;444:1027–131.
115. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 2007;56:1761–72.
116. Anhê FF, Varin TV, Le Barz M, Desjardins Y, Levy E, Roy D, et al. Gut microbiota dysbiosis in obesity-linked metabolic diseases and prebiotic potential of polyphenol-rich extracts. Curr Obes Rep. 2015;4:389–400.
117. Anhê FF, Pilon G, Roy D, Desjardins Y, Levy E, Marette A. Triggering Akkermansia with dietary polyphenols: a new weapon to combat the metabolic syndrome? Gut Microbes. 2016;7:146–53.
118. Ruel G, Pomerleau S, Couture P, Lamarche B, Couillard C. Changes in plasma antioxidant capacity and oxidized low-density lipoprotein levels in men after short-term cranberry juice consumption. Metabolism. 2005;54:856–61.
119. Ruel G, Lapointe A, Pomerleau S, Couture P, Lemieux S, Lamarche B, et al. Evidence that cranberry juice may improve augmentation index in overweight men. Nutr Res. 2013;33:41–9.