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REVIEW

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Strawberries, Blueberries, and Cranberries in the Metabolic Syndrome: Clinical Perspectives

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ABSTRACT: Emerging science supports therapeutic roles of strawberries, blueberries, and cranberries in metabolic syndrome, a prediabetic state characterized by several cardiovascular risk factors. Interventional studies reported by our group and others have demonstrated the following effects: strawberries lowering total and LDL-cholesterol, but not triglycerides, and decreasing surrogate biomarkers of atherosclerosis (malondialdehyde and adhesion molecules); blueberries lowering systolic and diastolic blood pressure and lipid oxidation and improving insulin resistance; and low-calorie cranberry juice selectively decreasing biomarkers of lipid oxidation (oxidized LDL) and inflammation (adhesion molecules) in metabolic syndrome. Mechanistic studies further explain these observations as up-regulation of endothelial nitric oxide synthase activity, reduction in renal oxidative damage, and inhibition of the activity of carbohydrate digestive enzymes or angiotensin-converting enzyme by these berries. These findings need confirmation in future studies with a focus on the effects of strawberry, blueberry, or cranberry intervention in clinical biomarkers and molecular mechanisms underlying the metabolic syndrome.

KEYWORDS: metabolic syndrome, strawberries, blueberries, cranberry juice, postprandial lipemia, hypertension, malondialdehyde

INTRODUCTION

Berry fruits, a rich source of micronutrients and several bioactive phytochemicals, have been recognized among all fruits and vegetables for their distinct cardiovascular health benefits.[1,2] Strawberries are among the most popular fresh fruits produced and consumed in the United States, followed by blueberries, whereas cranberries as juice and juice blends are also popular sources of phytochemicals in the U.S. diet.[2,3] The antioxidant properties of these berry fruits have been well documented in various in vitro, animal, and human studies, although the observed cardiovascular effects have been explained by mechanisms beyond antioxidant activity.[4] In comparative analyses of commonly consumed polyphenol-rich beverages in the United States, blueberry juice and cranberry juice were listed among the top ten beverages of high antioxidant potency measured as the sum of four assays [1,1-diphenyl-2-picrylhydrazyl radical (DPPH), oxygen radical absorbance capacity (ORAC), Trolox equivalent antioxidant capacity (TEAC), and ferric reducing ability of plasma (FRAP)]; strawberries were not included as a popular beverage in this study.[5] In another paper comparing antioxidant properties of fresh fruits as determined by cellular antioxidant activity (CAA), blueberries were shown to have the highest CAA values, whereas apples and strawberries were the largest contributors of CAA to the U.S. diet.[6] In a recently reported study identifying food sources and supplements of antioxidant activity in the U.S. diet, blueberries, strawberries, and cranberry juice drink were among the top major food items consumed by U.S. adults.[7]

As obesity, metabolic syndrome, and type 2 diabetes mellitus continue to plague U.S. society, the food and nutraceutical industries relentlessly pursue the identification and commercialization of medicinal foods and beverages to address these public health challenges. In this regard, berries have captured significant attention in the management of metabolic syndrome, identified as the prediabetic state represented by a clustering of cardiovascular risk factors, namely, abdominal adiposity, dyslipidemia (high triglycerides, low HDL), hypertension, and impaired fasting glucose. In addition, metabolic syndrome is also associated with elevated biomarkers of lipid oxidation and inflammation.[8,9] The role of berries in metabolic syndrome has been further defined by the largest observational study in berry consumption reported to date in a cohort of approximately 15700 adults.[10] In this paper, Cassidy et al. show an inverse association between strawberry and blueberry consumption and risks of hypertension, a salient feature of metabolic syndrome.[10] This observational finding is supported by various small-scale human intervention studies in healthy subjects or in obese adults with or without metabolic syndrome. Mechanistic studies further explain these clinical observations, which may be summarized as the following three principal cardiovascular effects of strawberries, blueberries, and cranberries: antioxidant, antihypertensive, and antiatherosclerotic activities. The objective of this minireview is to discuss the key findings from human interventional studies, including those reported by our group, along with pertinent mechanistic data that substantiate the emerging roles of strawberries, blueberries, and cranberries in metabolic syndrome.

STRAWBERRIES AND METABOLIC SYNDROME

Strawberries (*Fragaria* × *ananassa*) are a rich source of polyphenols, ellagitannins, vitamin C, folic acid, potassium, and fiber.

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Approximately 40 phenolic compounds have been identified in strawberries, among which vitamin C, ellagitannins, and anthocyanins were shown to be the most significant contributors to electrochemical responses, a marker of antioxidant capacity.[11] The effects of strawberries in lowering lipids, lipid oxidation, and postprandial hyperglycemia, hyperlipidemia, and inflammatory responses have been documented in human interventional studies in healthy subjects or in those with cardiovascular disease (CVD) risks, such as the metabolic syndrome. Fresh strawberry intervention in healthy subjects (240−300 g) has been shown to increase postprandial serum antioxidant capacity and vitamin C,[12,13] and strawberry jam (20 g) or mixed-berry puree (150 g) supplementation in healthy subjects has also been shown to attenuate postprandial hyperglycemia when compared to the controls receiving a matched glucose load.[14,15] In a similar postprandial study in hyperlipidemic adults, Burton-Freeman and colleagues demonstrated significant attenuation of postprandial lipemia and lipid oxidation by freeze-dried strawberry intervention (10 g/day ∼ 100 g fresh strawberries) following a high-fat meal challenge.[16] Postprandial (fed state) hyperglycemia and lipemia have been shown to be further exaggerated in the presence of visceral obesity, dyslipidemia, and impaired glucose metabolism, which constitute the key features of metabolic syndrome, than in healthy subjects.[17,18] Thus, these effects of strawberries in improving postprandial metabolism might have significant implications in the management of metabolic syndrome.

Few long-term feeding studies have been reported on the effects of strawberries in obese adults with metabolic syndrome. Thus, our group tested the hypothesis that freeze-dried strawberries (50 g/day ∼ 500 g fresh strawberries) will improve features of metabolic syndrome and associated lipid oxidation and inflammation in obese adults. Our key findings demonstrate a significant reduction in total and low-density lipoprotein (LDL)-cholesterol, small LDL particles, serum malondialdehyde, and adhesion molecules in strawberry-supplemented groups versus controls.[19,20] In fact, ours was the first study to show such lipid-lowering effects of strawberries in selected subjects with at least three features of metabolic syndrome, in comparison to previous studies showing a decrease in lipid oxidation or an increase in high-density lipoprotein (HDL) following strawberry (454 g) or mixed-berry intervention (2 portions including 100 g strawberry puree), respectively, in adults with CVD risk factors.[21,22] Elevated serum cholesterol and biomarkers, such as malondialdehyde and adhesion molecules, have been strongly associated with atherosclerosis and subsequent CVD.[23−25] Malondialdehyde, a naturally occurring product of lipid peroxidation, has been recognized in influencing the expression of various effector molecules of the immune system, promoting the recruitment of the cells of the innate and adaptive immune systems into the vessel wall. This aids in the development of atherosclerotic lesions.[26] Adhesion molecules further assist in recruitment of monocytes and their migration into the subendothelial space, which are key events in the progression of atherosclerotic lesions.[27] Thus, these preliminary clinical data suggest the potential antiatherosclerotic effects of strawberry consumption, especially in metabolic syndrome.

Mechanistic studies in cells and in animal models of obesity and diabetes have demonstrated the following treatment effects of strawberry fruits, extracts, or purified anthocyanins: upregulation of endothelial nitric oxide synthase (eNOS);[28] inhibition of glucose uptake and transport and normalizing blood glucose levels;[29,30] inhibition of carbohydrate and lipid digestive enzymes, especially α-glucosidase and α-amylase, and pancreatic lipase activity;[31,32] and also of angiotensin I-converting enzyme (ACE),[33] which may be linked to the therapeutic management of hyperglycemia and hypertension, the key features of metabolic syndrome. Thus, these clinical and mechanistic findings warrant further investigation, but provide promising data for selecting fresh or frozen strawberries in the dietary management of metabolic syndrome.

BLUEBERRIES AND METABOLIC SYNDROME

Highbush (*Vaccinium corymbosum*) and lowbush (*Vaccinium angustifolium* Aiton.) blueberries have been associated with several cardiovascular health benefits. Anthocyanins have been shown to be the main contributors to the antioxidant capacity of blueberries.[34] Chromatographic profiling has further shown that anthocyanins comprise approximately 35−74% total phenolic compounds in blueberries, followed by hydroxycinnamic acid derivatives, flavonols, and flavan-3-ols.[35] In addition, blueberries are also significant sources of folic acid, vitamin C, and fiber, which may act in concert with the blueberry polyphenols in exerting the observed cardiovascular health effects.

Similar to the postprandial effects observed with strawberries,[16] freeze-dried blueberries (100 g) have also been shown to counterbalance the oxidative stress responses to a fast-food style meal challenge in healthy adults.[36] Thus, with the exaggerated postprandial responses in the metabolic syndrome taken into consideration,[17,18] blueberries may also have significant implications in attenuating such responses when consumed concomitantly with high-fat meals. Few studies have examined the cardiovascular effects of blueberries in long-term feeding studies. A 3-week feeding study in smokers has shown the antioxidant effects of blueberries (250 g) in decreasing lipid hydroperoxides versus controls.[37] Because smoking is also associated with elevated lipid oxidation and inflammation as in the metabolic syndrome,[38] blueberry supplementation may be an effective therapy for oxidative stress in these conditions. In recent years, two reported human studies have demonstrated the antihypertensive and insulin-sensitizing effects of freeze-dried blueberries in obese adults with metabolic syndrome and in obese insulin-resistant adults, respectively. In the first study reported by our group, 50 g of freeze-dried blueberries (∼350 g fresh blueberries) supplemented for 8 weeks caused a significant reduction in systolic and diastolic blood pressure and markers of lipid oxidation, especially oxidized LDL and malondialdehyde versus controls.[39] In the second study, a 6-week treatment with 45 g of freeze-dried blueberries (∼315 g fresh blueberries) caused a significant improvement in insulin sensitivity, as assessed by the high-dose hyperinsulinemic−euglycemic clamp in obese adults.[40] These data show the potential of blueberries, at dietary achievable doses, in improving hypertension and insulin resistance associated with metabolic syndrome and warrant further investigation in larger studies.

Mechanistic studies in animal models of hypertension further explain the antihypertensive effects of blueberries. Dietary supplementation of 3% freeze-dried blueberries for 8 weeks was shown to decrease systolic blood pressure in spontaneously hypertensive stroke-prone (SHRSP) rats versus controls.[41] In addition, the study also showed a decrease in markers of renal oxidative stress in blueberry-fed rats versus controls, indicating protection against renal oxidative damage by blueberries. In another animal model of spontaneously hypertensive rats, 8% wild blueberry

Table 1. Summary of Human Clinical (Interventional) Studies with Strawberries, Blueberries, and Cranberries in Metabolic Syndrome

berry	dose	study sample	duration	effects[a]	ref
strawberry (freeze-dried) (California Strawberry Commission, USA)	10 g (400 mg polyphenols)	overweight hyperlipidemic adults (n = 24)	postprandial	decrease in postprandial lipemia and lipid oxidation vs placebo	Burton-Freeman et al.[16]
strawberry (freeze-dried) (California Strawberry Commission, USA)	50 g/day day (2006 mg polyphenols)	obese adults with metabolic syndrome (n = 27)	8 weeks	decrease in total cholesterol and LDL-C, small LDL particles and VCAM-1 vs controls	Basu et al.[19]
strawberry (freeze-dried) (California Strawberry Commission, USA)	50 g/day (2006 mg polyphenols)	obese adults with metabolic syndrome (n = 16)	4 weeks	decrease in total cholesterol and LDL-C and MDA	Basu et al.[20]
fresh strawberries (local market)	454 g/day (2000 mg polyphenols)	hyperlipidemic adults (n = 28)	10 weeks	decrease in oxidative damage to LDL vs baseline	Jenkins et al.[21]
mixed berries (bilberries, lingonberries, strawberries, chokeberry, raspberry) as fresh fruit, puree, and nectar (formulated by research personnel)	160 g/day (837 mg polyphenols)	overweight adults with cardiovascular risk factors (n = 72)	8 weeks	decrease in systolic blood pressure and increase in HDL-C vs controls	Erlund et al.[22]
blueberry (freeze-dried) (Highbush Blueberry Council, USA)	50 g/day (1624 mg polyphenols)	obese adults with metabolic syndrome (n = 48)	8 weeks	decrease in systolic and diastolic blood pressure and oxidized LDL and MDA vs controls	Basu et al.[39]
blueberry (freeze-dried) (Highbush Blueberry Council, USA)	45 g/day (1462 mg polyphenols)	obese insulin resistant adults (n = 32)	6 weeks	increase in insulin sensitivity vs placebo	Stull et al.[40]
low-calorie cranberry juice cocktail (Ocean Spray, Inc., USA)	125, 250, and 500 mL/day; 100, 200, and 400 mg total polyphenols, respectively	adults with abdominal obesity (n = 30)	three successive 4-week intervention periods	increase in plasma HDL-C and apolipoprotein AI following 250 mL juice/day vs baseline	Ruel et al.[48]
cranberry extracts (Triarco Industries Inc., USA)	1500 mg/day (total polyphenol content not reported)	overweight adults with type 2 diabetes (n = 30)	12 weeks	decrease in total cholesterol, LDL-C, and total cholesterol:HDL-C ratio vs placebo	Lee et al.[50]
cranberries (raw, sweetened, or low-calorie) (Ocean Spray, Inc., USA)	55 g raw cranberries; 40 g sweetened or low-calorie dried cranberries (total flavonols ~140 mg)	obese elderly adults with type 2 diabetes (n = 13)	postprandial	decrease in postprandial insulin and glucose vs controls	Wilson et al.[51]
low-calorie cranberry juice (Ocean Spray, Inc. USA)	480 mL/day (458 mg polyphenols)	obese adults with metabolic syndrome (n = 31)	8 weeks	increased plasma antioxidant capacity and decreased oxidized LDL and MDA vs placebo	Basu et al.[52]

[a] HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; MDA, malondialdehyde; VCAM-1, vascular cell adhesion molecule-1.

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supplementation significantly improved vasoconstriction and endothelial dysfunction.[42] Blueberries have also been shown to lower plasma ACE activity in SHRSP rats, suggesting another mechanism by which blueberries might be effective in the management of the early stages of hypertension.[43] In addition to decreasing elevated blood pressure, blueberries have also been demonstrated to decrease atherosclerotic lesions and up-regulate aortic expressions of antioxidant enzymes in apolipoprotein E-deficient mice.[44] In vitro studies have also reported blueberries to inhibit α-amylase and α-glucosidase activities with implications in the management of hyperglycemia.[45] Thus, these mechanistic findings deserve clinical translation in obesity and metabolic syndrome to identify optimal dosing and duration of blueberry intervention and the risk factors or pathological stage of CVD expected to be modulated by blueberries.

CRANBERRIES AND METABOLIC SYNDROME

Cranberries (*Vaccinium macrocarpon*) native to North America are a rich source of phenolic acids (benzoic, hydroxycinnamic, and ellagic acids) and flavonoids (anthocyanins, flavonols, and flavan-3-ols).[2] Comparative analyses of phenolic antioxidants among different cranberry products show the following order of antioxidant content: frozen > 100% juice > dried > 27% juice > sauce > jellied sauce.[46] Thus, on the basis of these data, dried cranberries and 27% cranberry juice, commonly consumed in the United States, are significant dietary sources of polyphenols.

Several human studies have reported the antioxidant, anti-inflammatory, and HDL-raising effects of cranberry juice supplementation in healthy or obese adults.[47−49] Cranberries have also been tested in patients with type 2 diabetes and have been shown to lower lipid profiles and postprandial hyperglycemia versus controls. In 2008, Lee et al. reported a significant decrease in total and LDL-cholesterol, as well as the total/HDL-cholesterol ratio following a 12-week administration of cranberry extracts (1500 mg/day), although blood glucose remained unaffected.[50] Wilson et al. also reported a postprandial study comparing the effects of sweetened or low-calorie dried cranberries (40 g), raw cranberries (55 g), and white bread (57 g) in glycemic response in patients with type 2 diabetes. The study revealed significantly lower postprandial insulin and glucose following low-calorie dried cranberries or raw cranberry intervention compared to regular sweetened cranberries or white bread (control).[51] Thus, the selection of low-calorie dried cranberries may provide a palatable source of polyphenols and fiber and also aid in producing favorable glycemic response in type 2 diabetes. Our group recently reported an 8-week double-blind randomized controlled trial in which low-calorie cranberry juice (27% juice, 480 mL/day) caused a significant increase in plasma antioxidant capacity and decreased plasma oxidized LDL and malondialdehyde in obese adults with metabolic syndrome, when compared to those consuming the placebo juice.[52] Both oxidized LDL and malondialdehyde have been shown to promote the genesis and progression of atherocslerosis, principally via immune system activation and endothelial dysfunction.[26,27] Thus, our study findings, in combination with others, provide evidence on the role of specific cranberry products, such as low-calorie cranberry juice or dried cranberries, in attenuating dyslipidemia, hyperglycemia, and biomarkers of atherosclerosis associated with metabolic syndrome. The role of cranberry extracts needs to be further examined for safety and efficacy in larger trials on metabolic syndrome or type 2 diabetes.

Mechanistic studies in animal models have also reported the vasodilatory effects of cranberry juice via induction of endothelial nitric oxide synthase (eNOS),[53] decrease in total and LDL-cholesterol in an animal model of familial hypercholesterolemia via inhibiting enzymes involved in lipid and lipoprotein metabolism,[54] and protection against chemotherapy-induced cardiac toxicity in rats via antioxidant activity.[55] Thus, these data need further investigation in support of the cardiovascular benefits of cranberry supplementation in metabolic syndrome.

BERRY BIOACTIVES IN THE METABOLIC SYNDROME: DOSE AND EFFECTS OF PROCESSING

As summarized in Table 1, the favorable outcomes in clinical features of the metabolic syndrome, namely, hypertension, insulin resistance, dyslipidemia, and lipid oxidation are produced with interventions using whole berries (dried or freeze-dried or fresh), and in some studies with low-calorie juice (no sugar added). Encapsulated cranberry extracts were shown to produce improvements in lipid profiles in type 2 diabetic patients in a single reported study. Furthermore, significant effects in these metabolic parameters were observed at a minimal berry polyphenol dose of 400 mg, corresponding to a minimum daily consumption of 1 cup of fresh berries or low-calorie berry juice (Table 1). It should also be noted that in addition to polyphenols, the administered berry doses in these studies were significant sources of several micronutrients and/or fiber, which may synergistically contribute to the observed health outcomes in the metabolic syndrome. Processing methods, such as drying, storage, and producing extracts and juices from strawberries, blueberries, and cranberries, have been shown to significantly reduce the total polyhenols, flavonoids, vitamin C, and antioxidant capacity of the berry products.[56−60] In contrast, freeze-dried or frozen strawberries or blueberries, administered in reported human interventional studies in the metabolic syndrome,[16,19,20,39,40] have been shown to retain maximum polyphenols and vitamins when compared to berries treated with other drying methods.[56,60] In the case of cranberries, juice and dried fruit forms, the most commonly consumed products associated with favorable effects in the metabolic syndrome,[48,51,52] however, have lower antioxidant content than fresh or frozen cranberries.[46,61] Thus, on the basis of these reported data, recommendations of fresh or frozen strawberries and blueberries and dried cranberries and low-calorie cranberry juice, readily available in the market, seem to be a prudent strategy to obtain the demonstrated health benefits of these berries in metabolic syndrome.

CONCLUSIONS AND FUTURE PERSPECTIVES

Thus, on the basis of accumulating scientific evidence, berries, especially strawberries, blueberries, and cranberries, may alleviate features of the metabolic syndrome, principally via antioxidant, antihypertensive, and antiatherosclerotic activity. Such observations are supported by postprandial, as well as long-term, interventional studies in healthy subjects or in those with metabolic syndrome or type 2 diabetes. Freeze-dried strawberries and blueberries have shown the ability to counterbalance the negative effects of a high-fat meal challenge by decreasing postprandial lipemia and oxidative stress. Low-calorie dried cranberries have also been demonstrated to produce a more favorable postprandial glycemic response when compared to a refined carbohydrate load. Thus, these berry products may improve postprandial metabolism that is typically exaggerated in the presence of metabolic

syndrome. Our study findings, specifically in obese adults with metabolic syndrome, reveal the antioxidant, serum cholesterol-lowering, and antihypertensive effects of strawberries, blueberries, and low-calorie cranberry juice. These findings, although novel and supported by mechanistic data, need further confirmation in larger trials. Future studies are needed in defining the optimal dose, form (as affected by processing methods), and duration of berry intervention in the management of metabolic syndrome and related cardiovascular risk factors. Such studies should also define the role of strawberries, blueberries, and cranberries in modulating specific biomarkers of oxidative stress and inflammation and molecular mechanisms underpinning the metabolic syndrome. Such efforts are urgently needed for effective dietary interventions involving berries to attenuate the risk factors associated with metabolic syndrome and its progression to more advanced forms of cardiovascular disease.

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