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Dietary berries, insulin resistance and type 2 diabetes: an overview of human feeding trials

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Abstract

Dietary berries are a rich source of several nutrients and phytochemicals and in recent years, accumulating evidence suggests they can reduce risks of several chronic diseases, including type 2 diabetes (T2D). The objective of this review is to summarize and discuss the role of dietary berries (taken as fresh, frozen, or other processed forms) on insulin resistance and biomarkers of T2D in human feeding studies. Reported feeding trials involve different berries taken in different forms, and consequently differences in nutritional or polyphenol composition must be considered in their interpretation. Commonly consumed berries, especially cranberries, blueberries, raspberries and strawberries, ameliorate postprandial hyperglycemia and hyperinsulinemia in overweight or obese adults with insulin resistance, and in adults with the metabolic syndrome (MetS). In non-acute long-term studies, these berries either alone, or in combination with other functional foods or dietary interventions, can improve glycemic and lipid profiles, blood pressure and surrogate markers of atherosclerosis. Studies specifically in people with T2D are few, and more knowledge is needed. Nevertheless, existing evidence, although sparse, suggests that berries have an emerging role in dietary strategies for the prevention of diabetes and its complications in adults. Despite the beneficial effects of berries on diabetes prevention and management, they must be consumed as part of a healthy and balanced diet.

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Conflicts of interest

The authors have no conflict of interest.

Introduction

Type 2 diabetes (T2D) is a global pandemic.[1,2] Pharmacologic interventions are costly and associated with adverse side effects, while nutritional therapy remains central to prevention, development and treatment. T2D is a metabolic disease that is characterized by chronic hyperglycemia due to the inability of the insulin-receptive cells of the body to effectively respond to insulin (insulin resistance) and/or insufficient insulin production by the beta cells of the pancreas (insulin insufficiency). When alterations in glucose metabolism initially arise, the insulin-secreting beta cells of the pancreas are often functioning optimally, but the insulin-sensitive tissues have started to become insensitive to the insulin being secreted.[3] It is thought that this desensitization to insulin is, in part, caused by insufficient insulin receptors on the normally insulin-sensitive target cells, preventing or decreasing the intracellular signaling and translocation of the glucose transporter (GLUT4) receptors to the cell membrane. This results in decreased glucose uptake by the insulin-sensitive tissues and leads to an increase in insulin output by the pancreatic beta cells to try and compensate for the rising blood glucose levels. The progressive deterioration in beta cell function, and reduction in the number of beta-cells, further elevates plasma glucose levels and contributes to the pathology of T2D.[4]

Nutrition therapy remains an integral part of diabetes management, recommended by the American Diabetes Association (ADA), and every other national diabetes organization. The role of plant-based diets, and the benefits of complex carbohydrates derived from fruits, vegetables, legumes and whole grains in the management of hyperglycemia and related cardio-metabolic risks have been consistently emphasized by ADA.[2] Dietary bioactive compounds, especially the polyphenolic flavonoids that are found in colorful fruits, vegetables, have shown consistent anti-diabetic effects in experimental models and human studies.[5–7] Among foods (and associated beverages) that have been extensively studied in recent years for their role in the management of chronic diseases, dietary berries deserve a special attention. Based on the National Health and Nutrition Examination Survey (NHANES, 2007–2012), berry intake comprised 10% of all fruit intake in US adults.[8] Berries, especially cranberries, blueberries, blackberries, raspberries and strawberries, are low in calories, and contain a range of micronutrients and antioxidants including vitamin C, folic acid, potassium, manganese, and polyphenols, such as anthocyanins, and tannins. All of these have been shown to exert health benefits in people with diabetes.[9,10] Several epidemiological studies have associated habitual consumption of bioactive compounds from berries with subsequently reduced risks of inflammation, T2D and cardiovascular disease (CVD).[5,6,11,12]

While several reports have described effects of dietary berry supplementation in improving cardio-metabolic risks in adults with pre-diabetes or T2D, their effects on glycemic control have been inconsistent. It is important to determine whether the type of berry and/or the way it is presented or processed, and/or the timing of intervention (*e.g.* postprandial *vs.* chronic), may explain differences in findings. This reviews aims to provide an overview of controlled interventional studies that have examined the effects of commonly-consumed dietary berries (whole, processed, or extracts) on glycemic control and related cardio-metabolic risks in healthy adults, those with features of the metabolic syndrome, and those with T2D.

Nutritional value of dietary berries

Dietary berries are low in calories, carbohydrates, and fats, and high in fiber, polyphenols, but contain certain essential micronutrients such as vitamin C, E and folic acid.[13] Berries are typically consumed as whole fruits or in processed forms including frozen and dried fruits, juices, dried powders, and concentrated extracts of bioactive constituents. The USDA Economic Research Service reported apples and oranges as the "top fruit choice" of US in 2016, but over half the combined pound-weight of both fruits was consumed as processed juice. Considering fresh and frozen fruit consumption, strawberry pound-weight (~3.9 and ~1.4 pounds per capita, respectively) actually "outweighed" oranges (~3.5 pounds per capita).[14] Berries that are common in the US diet include cranberries, strawberries, blueberries, blackberries, and raspberries. Based on the USDA Food Composition Database, fresh whole berries are an excellent source of vitamin C and manganese, with a 100 g serving providing ~64% and ~21% of RDA respectively. Blackberries and blueberries are an excellent source of vitamin K, providing ~20% of RDA per 100 g serving; additionally, they are considered a good source of fiber, providing ~4 g for every ~50 kcals, with total sugar content averaging ~6 g per 100 g whole fruit.[15]

Major categories of polyphenolic flavonoids present in berries include flavan-3-ols, flavanols, and anthocyanidins, such as cyanidin and delphinidin. The latter account for the blue, red, and purple colors of berries. Polyphenol levels vary depending on the variety of the fruit and the processing it has undergone. The USDA Database for Flavonoid Content of Selected Foods summarizes mean flavonoid content for commonly consumed berry products.[16] In the raw forms of commonly consumed berries, the average total anthocyanin content is ~68 mg per 100 g for cranberries, 53 mg per 100 g serving for blueberries, 47 mg per 100 g for raspberries, and 2 mg per 100 g for strawberries. A striking difference in flavonoid content may be identified when comparing raw blueberry with raw bilberry (of the same genus *Vaccinium i.e.* "the European blueberry"); bilberry anthocyanins averaging ~174% the amount found in blueberry, and raw bilberries contain 20-fold more cyanidin (85 mg per 100 g *vs.* 4 mg per 100 g) and four-fold more delphinidin (97 mg per 100 g *vs.* 21 mg per 100 g) than an equal weight of blueberries.[16] In addition to anthocyanins being the most predominant flavonoids in berries, flavan-3-ols and flavonols are also present in smaller quantities as follows: raw blackberries ~42 mg and 4.5 mg; raw highbush blueberries~6.3 mg and 11 mg; raw cranberries ~6.5 mg and 22 mg; raw raspberries ~6 mg and 1 mg; raw strawberries ~4.5 mg and 2 mg flavan-3-ols and flavonols, respectively per 100 g whole fruit.[16]

Anthocyanin content appears to be particularly affected by processing. For example, frozen strawberries, blueberries, and raspberries demonstrated an average ~42% decrease in anthocyanin content compared with their raw forms, while raspberry purees average a ~60% decrease. Similarly, juices of strawberries, cranberries, and raspberries retain only ~22% of anthocyanin contents when compared to their raw whole fruit forms.[16] Processing methods, such as storage temperature and duration, as well as heat treatment, may significantly degrade anthocyanins in comparison with other flavonoids,[17] while freeze-drying seems the most effective way to preserve anthocyanins in strawberries.[18] Freeze-dried berries have been widely used in feeding trials, including our own.[19–22] In addition to the methods of

processing, seasonal variations and time of harvest have also been shown to influence different berry cultivars. For example, summer strawberry cultivars reveal higher phenolic compounds than winter versions,[23] whereas, late harvest *vs.* early harvest has been shown to significantly increase phenolic content of blueberries.[24] Also, agricultural practices which may vary across geographic regions may influence phenolic composition; organic practices have been shown to yield blackberries with higher phenolic content than conventional farming practices.[25] The wide variability in flavonoid composition in berries and their processed forms should be considered in clinical studies, especially in the interpretation of effects on clinical outcomes.

Effects of berries on glycemia and insulin resistance in healthy adults

As summarized in Table 1, dietary (including beverage) supplementation with berries, with or without matching for carbohydrate intake, significantly improved postprandial insulin responses, blunting postprandial insulin and glucose responses in metabolically healthy adults. These postprandial studies used either one type of berry or a combination of different berries including blueberry, bilberry (European blueberry), cloudberry, chokeberry, cranberry, lingonberry, raspberry, and strawberry. Of these studies, the two that used concentrated blueberry powder alone reported modulation of gastrointestinal hormones related to appetite, *e.g.* pancreatic polypeptide, and a delayed glycemic response in the treatment *vs.* control phase.[26,27] Interestingly, these two studies did not show any effects on postprandial glucose and insulin excursions.[26,27] Gastrointestinal hormones modulate hunger, satiety, and metabolic responses including glycemia. There are two distinct types of neurons with appetite-stimulating peptides and appetite-inhibiting peptides. The peptides they release act as neurotransmitters controlling feelings of hunger and satiety. Pancreatic polypeptide decreases gastric emptying and reduces pancreatic exocrine secretion, and thus plays an important role in satiety.[28,29] Glucagon-like peptide-1 (GLP-1), secreted by enteroendocrine cells contribute to meal-related glycemic control by stimulating insulin secretion, inhibiting glucagon secretion, slowing gastric emptying, and reducing hepatic glucose metabolism.[30,31] Preliminary data provide evidence on a role for blueberries in modulation of postprandial glycemia through effects on GI hormones in healthy adults,[26,27] and need further investigation in adults with insulin resistance and T2D. Furthermore, the hypothalamus has a major role in the regulation of energy homeostasis.[32] The arcuate nucleus (Arc) contains the first-order neurons in the hypothalamus in response to the peripheral signals of energy stores and satiety. Neurons that express proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) in the hypothalamic Arc suppress feeding and increase energy expenditure in response to circulating adiposity signals such as leptin.[33,34] There is an emerging role of dietary bioactive compounds, such as tea polyphenols, as well as resveratrol present in berries in counteracting leptin resistance by increasing expression of POMC and decreasing neuropeptide Y/agouti-related peptide, thereby decreasing food intake.[35] These mechanisms are of relevance to obesity, impaired glucose tolerance and insulin resistance that could be potentially reversed or attenuated by a diet enriched with berries.

The delayed postprandial glucose responses elicited by blueberry ingestion may be mediated by anthocyanin-inhibition of intestinal alpha-amylase and alpha-glucosidase activity (that

has been observed *in vitro*),[36,37] thereby slowing the rate of carbohydrate digestion. Anthocyanins have also been shown to cause inhibition of glucose transport from the intestine to plasma, specifically by inhibiting the sodium glucose co-transporter 1 (SGLT1) and the glucose transporter GLUT2.[38]

Studies reported by Törrönen *et al.* demonstrate efficacy of a combination of berries, taken in feasible daily amounts, in counteracting the hyperglycemic effect of carbohydrates such as white bread, rye bread or added table sugar in healthy adults. In these studies, consumption of berries together with the carbohydrate load significantly decreased postprandial glucose and insulin responses.[39,40] A reduction in postprandial insulin prevents reactive hypoglycemia and lowers levels of free fatty acids and stress hormones, features often seen during the late postprandial period after consumption of refined carbohydrates.[41] Regular consumption of diets incorporating berries may thus reduce first-phase insulin secretion (mainly by decreasing carbohydrate absorption by inhibiting α-amylase and α-glucosidase, and thereby glucose availability),[36,37] improve and preserve pancreatic β-cell function, principally *via* decreasing oxidative stress and inflammation that can be attributed to the function of anthocyanins.[42–44] In addition to the polyphenol content, whole berries are also a rich source of fiber that has been shown to delay gastric emptying and decrease glucose absorption that subsequently lead to decreases in postprandial rise of blood glucose.[45,46] In a Swedish study on the effects of a combination of berries, prebiotics and probiotics, a fermented oatmeal beverage was administered with *vs.* without bilberries or rosehip, and postprandial glucose and insulin levels were determined. Significantly lower postprandial insulin was observed in the low- (10%) and high- (47%) dose supplementation. The fermented oatmeal drink elicited a high glycemic response and this was significantly blunted by bilberry supplementation.[47]

These clinical observations are complemented by mechanistic data supporting anti-diabetic effects of fermented blueberry juice in mice.[48] In this rodent model of obesity and leptin resistance, treatment of fermented blueberry juice for four weeks (40 mL per kg body weight) significantly decreased glucose response to an oral glucose load and improved insulin sensitivity when compared to the control group.[48] Also, treatment of cells with fermented blueberry juice increased glucose uptake in mouse myoblasts, and in 3T3-L1 adipocytes, whereas non-fermented juice had no effect on glucose transport. Treatment of cells with fermented blueberry juice was also shown to activate AMP-activated protein kinase (AMPK) in the same study.[49] AMPK is an energy sensing protein kinase and an important regulator of anabolic and catabolic processes and consequently metabolic homeostasis.[50] AMPK has been shown to exhibit anti-inflammatory effects, and especially ameliorate fatty acid-induced inflammation in the liver that upregulates pro-inflammatory cytokines involved in insulin resistance.[51] The data suggest that an insulin-independent pathway may underlie increased glucose uptake. Dietary polyphenols undergo extensive metabolism by tissues and the microbiota, leading to the formation of several metabolites many of which have poor bioavailability in humans.[22,52–54] Thus, findings from pre-clinical models using cells have limited application to human and must be confirmed in animal models and clinical trials. Based on these preliminary findings, and keeping in view the high fruit juice consumption in the adult population globally,[55] fermented berry juices must be further investigated for their role in glycemic control in clinical trials.

Effects of berries on glycemia and insulin resistance in overweight and obese adults

Being overweight or obese is associated with insulin resistance, dyslipidemia and increased risk of T2D and related cardiovascular complications.[56] Dietary berries have been shown to improve insulin resistance in overweight and obese adults, especially those with insulin resistance as documented by HOMA-IR of greater than 2.0. As summarized in Table 2, dietary cranberries, blackberries, blueberries, strawberries, alone or in combination, may improve insulin resistance in overweight and obesity: as witnessed by some, but not in all, studies. Differences in composition of berry polyphenols and/or study design may contribute to the differences. In a dose-response postprandial study involving adults with abdominal adiposity and insulin resistance, supplementation of 40 g freeze-dried strawberries (FDS) at breakfast ameliorated '6 h postprandial hyperinsulinemia' by approximately 12.5% when compared to meal only. The 6 h postprandial glucose levels did not differ among four groups: 0, 10, 20 and 40 g FDS.[22] In another study in a similar cohort, supplementation of a beverage with the highest dose of blackcurrant anthocyanins (600 mg) inhibited the rate of increase of post-prandial plasma glucose: it also lowered insulin concentrations in the first 30 minutes, had an inhibitory effect on plasma GIP concentrations up to 90 minutes, and reduced plasma GLP-1 concentrations at 90 minutes; however lower doses (300, 150 mg) had no significant inhibitory effects.[57] Thus, dietary berries at high doses may be effective in lowering postprandial hyperglycemia and hyperinsulinemia when administered with a mixed breakfast meal in overweight adults.

In chronic feeding studies (~12 to 24 weeks) we observed different effects of berries on markers of glycemic control. In our reported studies of obese adults with impaired fasting glucose and/or insulin resistance (HOMA-IR > 2.0), and in obese adults with a clinical diagnosis of knee osteoarthritis, low-(25 g) or high-dose (50 g) FDS showed no effect on insulin resistance or fasting blood glucose.[21,58] On the other hand, FDS decreased total and LDL-cholesterol, small LDL particles and inflammatory biomarkers, as well as mitigating knee OA pain in the treated vs. control group. Since "diabetic dyslipidemia" (high triglycerides, increased 'small LDL', and low HDL) has been significantly associated with CVD,[59] these findings are of clinical relevance, supporting a role for strawberries in reducing CVD risk in overweight and obese adults with impaired lipid profiles. Furthermore, controlled feeding studies using blueberries or low-calorie cranberry juice showed an improvement in insulin resistance and/or fasting glucose in overweight and obese adults. In a six-week feeding study of 45 g freeze-dried blueberries in obese adults with insulin resistance, a significant increase of approximately 22% in insulin sensitivity (determined by exogenous glucose infusion divided by fat-free mass) was observed in treated *vs.* placebo groups.[19] A strength of this study was the use of the most precise metabolic technique for assessing whole-body insulin sensitivity, *i.e.*, hyperinsulinemic-euglycemic clamps, a technique not reported in other chronic feeding studies with berries.[19] In an eight-week controlled feeding trial in which all meals were provided by the research group, supplementation of 480 mL cranberry juice twice a day improved HOMA-IR for those with higher baseline values (>2.0), suggesting improved glucose tolerance for overweight and obese adults.[60]

These findings are supported by animal studies; rats fed a high-fructose diet supplemented with cranberry powder had lower fasting glucose and insulin and improved HOMA-IR and β-cell function.[61] In other studies, berries in combination with other functional foods and bioactive compounds, such as bilberries combined with sea buckthorn, or in combination with other fruits and vegetables, improved biomarkers of antioxidant status and inflammation, but did not alter blood glucose or insulin resistance.[62,63] These data provide some evidence that in overweight and obese adults, berries may be protective against the development of T2D by improving insulin resistance, dyslipidemia and inflammation.

Effects of berries on glycemia and insulin resistance in adults with metabolic syndrome

Metabolic syndrome (MetS) comprises a constellation of risk factors for T2D and cardiovascular disease.[64] Our group and others have examined the effects of dietary berries in whole and processed forms in adults with MetS or 'pre-diabetes' (Table 3). We conducted a randomized controlled trial using freeze-dried blueberries (50 g day^{-1}) for eight weeks in adults who met three criteria of the MetS, most frequently large waist circumference, low HDL-C and elevated blood pressure.[20] Blueberries significantly decreased systolic and diastolic blood pressures, reduced plasma levels of lipid peroxidation products, but had no effects on blood glucose, HOMA-IR or inflammation.[20] We conducted another study using FDS (50 g day^{-1}) for eight weeks in a similar cohort, and observed a significant decreases in circulating adhesion molecules, total and LDL-C, but no effects on MetS-specific biomarkers.[65] These clinical observations are further explained by mechanistic data from animal models of hypertension showing that blueberry supplementation lowered blood pressure and improved renal oxidative stress, and that berry anthocyanins lowered blood lipids.[66,67]

Dietary cranberries are commonly consumed as juice; cranberry juice cocktail is a popular beverage in the US with health benefits distinct from other fruit juices or sugar-sweetened beverages. Based on the cross-sectional NHANES survey (2005–2008), adults consuming cranberry juice had a significantly lower serum C-reactive protein (CRP) compared to nonconsumers in a model adjusted for relevant covariates, including body mass index.[68] In concert, cranberry extracts exhibited anti-inflammatory effects in animal models of hepatic inflammation and obesity.[52,69] These findings are significant in view of the growing global burden of MetS or pre-diabetes, conditions are characterized by insulin resistance, mediated at least in part by a pro-inflammatory state.[64] We and others have examined the effects of low calorie cranberry juice in adults with MetS and observed significant antioxidant and anti-inflammatory effects, with no detrimental effects on glycemic profile. In an eight-week study, supplementation of 480 mL cranberry juice decreased oxidized LDL and lipid peroxidation,[70] and in another study of similar duration, a larger dose of cranberry juice supplementation (700 mL) increased adiponectin and folic acid, corresponding to anti-inflammatory effects in these adults.[71] Anti-inflammatory effects were also observed in human studies of MetS when bilberries were added to a healthy diet,[72] or following supplementation with acai berries[73] or Colombian blueberries.[74] On the other hand, dietary berries did not affect blood glucose or insulin resistance in these non-acute feeding studies

of people with MetS. The null effects on glycemic control may be explained by normal glucose profiles at baseline, despite the presence of MetS. In a recent report based on ten-year NHANES data in approximately 32 000 US adults, the prevalence of MetS was observed to be constant, while obesity and T2D have increased significantly.[75] Based on the observational data on the association of berry bioactive compounds, especially flavonoids with lower fat mass in women,[76] there is an urgent need to examine the role of berries in this public health burden of obesity and metabolic dysfunction.

Few postprandial studies examining the effects of berries in MetS have been reported. In pre-diabetic adults with insulin resistance (HOMA-IR > 2.0), low dose (125 g) and high dose (250 g) frozen red raspberries with a breakfast meal were shown to lower postprandial insulin, and the high dose also lowered peak glucose and 2 h-glucose load.[77] These findings are promising and warrant further studies on the effects of berries on postprandial metabolism in MetS. Overall, dietary berries may modulate glycemic profile selectively in adults with MetS who are insulin resistant, but generally exert anti-inflammatory and antioxidant effects and improve lipid profiles.

Effects of berries on glycemia and insulin resistance in adults with T2D

There are limited data on the effects of dietary berries in adults with diabetes, and results may be confounded by duration of diabetes, medications, and other complications of diabetes, notably renal impairment. As summarized in Table 4, we conducted feeding trials to examine the effects of dried cranberries and raspberries on postprandial metabolism. In diabetes, the postprandial phase is characterized by abnormal increases in plasma glucose and triglycerides, which contribute to endothelial dysfunction, oxidative stress and inflammation. Thus, reducing the magnitude of postprandial hyperglycemia, hypertriglyceridemia, oxidative stress and inflammation are goals of food-based nutritional interventions.[78] While meals high in fat and refined carbohydrate have been shown to elicit higher postprandial glycemia, co-administration of antioxidant micronutrients, as well as dietary bioactive compounds, such as fruit and wine polyphenols, has been shown to ameliorate adverse metabolic changes.[79] In our study, acute feeding of 40 g reduced-calorie dried cranberries together with a high-fat, ‘fast food style’ breakfast yielded significant 16% and 14% reductions in postprandial glucose at 2 h and 4 h, respectively. In addition, the cranberry supplement also reduced circulating IL-18 and lipid peroxidation products at the same time points. Cranberries present a combination of indigestible carbohydrates, soluble fiber and polyphenols: all are potential contributors to their effects in suppressing the postprandial increase of blood glucose in people with diabetes.[80] Wilson *et al.* also reported the role of raw and low-calorie dried cranberries in decreasing postprandial blood glucose and insulin when compared following ingestion of white bread in adults with T2D.[81] The findings were in concert with those from a 12-week study from Iran, in which daily consumption of one cup cranberry juice (240 mL) was associated with a significant 13% reduction of fasting blood glucose at 12 weeks.[82] The composition of cranberry polyphenols, which include the highest content of procyanidins among berries, and in addition soluble fiber, may have unique benefits in T2D. These effects merit further exploration in people with diabetes at different levels of glycemic control. Among other commonly-consumed berries, we reported the effects of frozen raspberries in decreasing

postprandial glucose and inflammatory biomarkers in T2D adults.[83] Raspberries have been previously shown to decrease postprandial insulin and glucose in adults with insulin resistance and MetS,[77] and in this work, we concluded that raspberries may have a distinct role in ameliorating postprandial dysglycemia in T2D as well.

In long-term feeding studies (six to 12 weeks), dietary berries and their extracts reduced glycemia and inflammation in adults with diabetes (Table 4). However, the data are too limited and heterogeneous to draw any conclusions about a single berry fruit in diabetes management. In a six-week study conducted in Iran, supplementation of a large dose of FDS (50 g day^{-1}) was associated with significant decreases in HbA1c and in biomarkers of inflammation and oxidative stress.[84] In another 12-week study of adults with newly diagnosed T2D, anthocyanin supplements from bilberries and blackcurrants (vs. placebo) decreased HbA1c to the level below threshold for diagnosing T2D.[85] HbA1c reflects the average glucose level during the past three months, and has the advantage of much lower variability than plasma levels of glucose or insulin.[86] The reduction in HbA1c is of clinical relevance, based on epidemiological evidence that intensive management glycemia reduces long-term microvascular and macrovascular complications of diabetes.[87] Other less commonly consumed berries, such as barberries and goji berries also improve blood glucose, lipids and/or blood pressure, but with no effects on HbA1c.[88,89] These data from human intervention trials conform to observational data on the inverse associations of dietary berry and/or berry flavonoid consumption with risk of T2D in cohort studies.[6,12] While promising, these findings require further investigation in people with diabetes at different ages, and with differing glycemic control, complication status, and disease duration.

Effects of berry extracts on glycemia and insulin resistance in adults with cardio-metabolic risks

Use of dietary supplements in adults with chronic diseases has been on the rise globally, but is often based on individual beliefs and perceptions that are based on inadequate knowledge of product quality, efficacy and safety. We reviewed studies examining the effects of berry-based dietary supplements in adults with pre-diabetes, T2D or related cardio-metabolic risks (Table 5). Supplementation of black raspberry extracts in a large dose (1800 mg day^{-1}) vs. placebo for 12 weeks decreased postprandial glucose based on a 75 g oral glucose tolerance test in adults with pre-diabetes (−28.1 ± 42.4 vs. +13.4 ± 52.6 mg dL^{-1}, respectively, $p < 0.05$), and also decreased surrogate markers of atherosclerosis in these adults.[90] Blood glucose was also reported to be decreased following supplementation with extracts of maqui berry (a native of Chile) (Delphinol), and by anthocyanin extracts from bilberry and black currants in two studies of adults with prediabetes[91,92] and in a single study of T2D, respectively.[93] These studies also reported improvement in ‘diabetic dyslipidemia’, with a significant decrease in LDL-C and an increase in HDL-C following berry extract supplementation. Li *et al.* (2015) reported an increase in circulating adiponectin levels following supplementation of anthocyanin extracts (320 mg) for 24 weeks.[93] Adiponectin is known to have insulin-sensitizing properties, and serum levels are decreased in insulin-resistant, diabetic, and obese subjects.[94] Thus, adiponectin has often been considered a critical target in the development of therapeutic strategies for diabetes. Induction of

adiponectin expression by the anthocyanin, cyanidin-3-O-β-glucoside, has been reported in animal studies.[95]

Consistent a beneficial role of cranberries in T2D,[60,70,81] Lee *et al.* (2008)[96] reported that 12-week cranberry extract supplementation improved lipid profiles in T2D patients but had no effects on blood glucose and HbA1c.[96] In summary, dietary supplementation with berry extracts may improve glucose and lipid profiles in people with diabetes, but the data are limited and do not address how isolated anthocyanins and bioactive compounds unique to different berries may modulate these effects. Furthermore, native berries such as maqui, mostly used for medicinal purposes in South American countries,[97] may exert significant interactions with oral diabetes drugs that have not been addressed in the reported data.

Recommendations and conclusions

Berry consumption, especially the commonly consumed blueberries, cranberries, strawberries and raspberries, may exert unique beneficial effects in diabetes management, mainly by improving glycemic and lipid profiles, increasing antioxidant status and decreasing biomarkers of atherosclerosis. In a meta-analysis of 22 randomized controlled trials (n = 1251) assessing effects of dietary berries in China, Korea, USA, and Europe, Huang *et al.* (2016)[98] reported the following significant positive outcomes that are relevant to diabetes management even though most subjects did not have diabetes: decreases in LDL-C by 0.21 mmol L^{-1}; systolic blood pressure by 2.72 mmHg; fasting glucose by 0.10 mmol L^{-1}; body mass index by 0.36 kg m^{-2}; HbA1c by 0.20%; and tumor necrosis factor-α by 0.99 pg mL^{-1}.[98] Although this meta-analysis involved 22 trials, only two were conducted in people who actually had diabetes. Nine of the 22 studies involved supplementation with cranberries; the others used blueberries, bilberries, black currants, black raspberries, elderberries, lingonberries, and whortleberries. Cranberries, with their high proanthocyanidin content, are perhaps the best characterized of all berries for health benefits, and have been shown to have many beneficial effects as outlined above, and also including protection of gut barrier integrity impairment and improvement of the microbiome.[80] Based on the findings summarized in Tables 1–5, generally consistent effects to those observed with cranberries are also observed with blueberries, bilberries, raspberries and strawberries. In general, berry consumption improved postprandial insulin and glucose profiles in healthy adults, those with insulin resistance and/or MetS, and those with T2D. In most studies including our own, beneficial effects were demonstrated with fresh, frozen or dried berries in the daily dosage range of 40–250 g, which is feasible for daily consumption. Other studies used freeze-dried berries at higher doses (~50 g, equivalent to 500 g fresh fruit), but this may only be feasible for a defined therapeutic period. Most of the long-term studies used commonly-consumed berries and addressed effects in overweight or obese subjects with insulin resistance, or with the MetS; only a few studies addressed T2D and more are needed, including studies to assess efficacy for weight loss.[2] Overall, from existing evidence, dietary berries, especially taken as fresh or frozen fruit, or as unsweetened juices or purees, may be recommended as part of a healthy dietary strategy for diabetes prevention and management.

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Biography

Aaron Calvano

Aaron R. Calvano graduated Magna Cum Laude from the University of Nevada, Las Vegas with a BS in Nutrition Sciences and Kinesiology. Aaron served as a leader in the UNLV Student Nutrition and Dietetic Association as chair, peer mentor, and researcher with the Nevada INBRE Undergraduate Research Opportunity Program. Aaron works as a research assistant and is currently participating in the UNLV dietetic internship program. Upon attaining the RDN credential, Aaron intends to gain further training in clinical research, and the practice of nutrition and dietetics.

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Dr Ken Izuora is an associate professor at the UNLV School of Medicine. He is the director of the UNLV Medicine Diabetes Center and section chief of the division of endocrinology. He received his medical degree from the University of Nigeria, completed residency training at Unity Health Program of University of Rochester, New York and endocrinology fellowship at Emory University, Atlanta. He is board certified in endocrinology and is a Fellow of the American College of Endocrinology. His research focuses on diabetes mellitus and its complications with interest in exploring the relationship between inflammation and these complications.

Edwin C. Oh

Dr Edwin Oh is an associate professor in the School of Medicine and the Nevada Institute of Personalized Medicine. Dr Oh received his Ph.D. in Neuroscience from the University of

Michigan at Ann Arbor. Following a postdoctoral fellowship at Johns Hopkins University, he served as an assistant professor in the Department of Neurology at Duke University. Dr Oh's research program focuses on the genetic and structural variants that contribute to human health and disease, the interpretation of such variation to improve the cellular and molecular diagnosis of genetic diseases, and the development of therapeutic paradigms.

Jeffrey L. Ebersole

Dr Jeffrey Ebersole is the associate dean for research at the School of Dental Medicine. He is an expert in oral immunology and is an active mentor for faculty and students. His research emphasizes studies of host-pathogen interactions using animal (rodents, nonhuman primates) and human models of oral disease(s). Dr Ebersole has ongoing cell biology studies related to host responses to oral infections, include a novel model of oral biofilms interacting with epithelial cells, and studies examining macrophage and dendritic cell biology particularly targeting oral pathogen/commensal bacterial interaction with these cells and resulting unique inflammatory responses and viral reactivation processes.

Timothy J. Lyons

Dr Timothy J Lyons, MD, is an Endocrinology specialist in Charleston, South Carolina. He attended and graduated from medical school in Belfast, Ireland in 1977, having over 42 years of diverse experience, especially in Endocrinology. He is affiliated with many hospitals including MUSC Medical Center. Dr Lyons is a physician scientist with more than 30 years of experience in conducting clinical and basic science research on the pathogenesis and complications of diabetes. He is one of the key investigators of landmark trials, such as the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes that has led to important findings underlying the management of diabetes.

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Dr Basu earned her master's in food & nutrition from University of Calcutta in India, a master's in Public Health (Epidemiology) from the University of South Florida, and her Ph.D. in nutrition from Texas Woman's University. She completed her postdoctoral fellowship in clinical nutrition at University of California Davis Medical Center. Dr Basu's research focuses on understanding the health effects of dietary bioactive compounds in modulating disease biomarkers in type 2 diabetes, hypertension, and related cardiovascular diseases. She has conducted several clinical trials focused on these foods, beverages, and dietary supplements among adults with the metabolic syndrome, type 2 diabetes, and cardiovascular risks.

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Table 1

Clinical studies on the effects of berries on glycemia and insulin resistance in healthy adults

Reference (year)	Participants	Study design	Intervention	Significant findings
Stote *et al.* (2019)[26]	Healthy adults sample size: *n* = 17	Randomized, placebo-controlled, crossover, 2 h-postprandial study	Standardized high-CHO breakfast with whole blueberries 140 g (Tx1); or calorie, sugars-, and fiber-matched placebo gel devoid of polyphenols (Cx1)	↑Pancreatic polypeptide concentrations in Tx1
Bell *et al.* (2017)[27]	Healthy young adults sample size: n = 17	Double-blind, five crossover studies of 2.5 h-postprandial studies	Blueberry powder 34 g beverages with anthocyanin contents 310 mg (Tx1), with sugar-matched variant (Tx2); or blueberry powder 80 g sugar-matched beverage with anthocyanin contents 724 mg (Tx3); or no-added-sugar control beverage (Cx1); or sugar-matched control beverage (Cx2)	Delayed postprandial phase of glucose response in Tx1, Tx2, and Tx3
Törrönen *et al.* (2013)[40]	Healthy adult females sample sizes: *n* = 13–20	Three single-blinded, randomized, controlled, crossover 2 h - postprandial studies	Study 1: Strawberry, bilberry, or lingonberry puree 150 g with white bread 50 g (Tx1) or rye bread 50 g (Tx2) Study 2: Raspberry, cloudberry, or chokeberry puree 150 g with white bread 50 g (Tx3) or rye bread 50 g (Tx4) Study 3: Strawberry, bilberry, cranberry, and blackcurrant mixture at 37.5 g per berry with white bread 50 g (Tx5) or rye bread 50 g (Tx6)	↓Postprandial insulin response in Tx1, Tx3, Tx5, and Tx6 ↑Glycemic profile improvements in Tx5 and Tx6
Törrönen *et al.* (2012)[39]	Healthy adult females sample size: *n* = 20	Randomized, controlled, crossover five 2 h-postprandial meal studies	Whole blackcurrant puree 150 g (Tx1); or whole lingonberry puree 150 g (Tx2); or blackcurrant nectar 300 mL with added sucrose 35 g (Tx3); or lingonberry nectar 300 mL with added sucrose 35 g (Tx4); or sucrose 35 g control meal (Cx1)	↓Insulin, glucose, FFA rebound and ↑glycemic profile improvements in all Tx groups
Granfeldt *et al.* (2011)[47]	Healthy young adults sample sizes: *n* = 9–11	Two series 2 h-postprandial meal studies	Series 1: Bilberry and fermented oatmeal drink 302 g with reference bread ~70 g (Tx1); or rose-hip and fermented oatmeal drink 300 g with reference bread ~70 g (Tx2)	↓Insulin index in Tx1
			Series 2: Bilberry and fermented oatmeal drink 270.3 g with reference bread 70 g (Tx3); or fermented oatmeal drink 270.3 g with reference bread 70 g (Tx4); or bilberry and fermented oatmeal drink 270.3 g with added whole homogenized bilberries 127.5 g and reference bread 70 g (Tx5)	↑Insulin sensitivity in Tx3 ↓insulin response Tx4 and Tx5

CHO: Carbohydrate, Cx: control group, FFA: free fatty acid, Tx: treatment group.

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Table 2

Clinical studies on the effects of dietary berry intervention (fresh or processed whole berries and juice) on insulin resistance in overweight/obese adults with cardio-metabolic risks

Reference (year)	Participants	Study design	Intervention	Significant findings
Solverson *et al.* (2018)[99]	Adult males with a BMI > 25 kg m^{-2}, nondiabetic, nonsmokers, fasting BG < 126 mg dL^{-1}; fasting TGs < 300 mg dL^{-1}; free of gastrointestinal, metabolic, and CVD; sample size: n = 27	Randomized, placebo-controlled crossover parallel-arm study	Whole blackberry 600 g day^{-1} (Tx1); or a calorie-matched artificially-flavored gelatin with high fat diet (Cx1) for seven days	↓Respiratory quotient and insulin AUC in Tx1 ↑Insulin sensitivity in Tx1
de Mello *et al.* (2017)[100]	Adults with FBG 5.6–6.9 mmol L^{-1}, and any two of the following: BMI 26–39 kg m^{-2}; large WC; serum TGs > 1.7 mmol L^{-1}; HDL < 1.0 mmol L^{-1} (men) or < 1.3 mmol L^{-1} (women); BP ≥ 130/≥85 mmHg; nondiabetic, free of terminal chronic disease; Sample size: n = 47	Randomized, controlled, triple-arm study	Bilberry 400 g day^{-1} fresh-equivalent (Tx1); or strawberries 100 g day^{-1} + raspberries 100 g day^{-1} + cloudberries 100 g day^{-1}(Tx2); or diet containing ≤80 g day^{-1} fresh berries (Cx1) for eight weeks	↑Serum hippuric acid, insulin sensitivity and ↓FPG in Tx1
Nilsson *et al.* (2017)[101]	Adults, nonsmoking; BMI ≤ 28 kg m^{-2}; FBG ≤ 6.1 mmol L^{-1}; free of known metabolic disorders, GI disorder or known cognitive disorders; sample size: n = 40	Randomized, controlled, crossover parallel-arm study	Berry beverage: 150 g blueberries + 50 g blackcurrant + 50 g elderberry + 50 g lingonberry + 50 g strawberry + 100 g tomatoes (Tx1); or water-based calorie-, pH-, and volume-matched control beverage (Cx1) for five weeks	↓Total- and LDL-C from baseline and compared to control in Tx1 ↑BG and insulin in Cx1 compared to Tx1
Paquette *et al.* (2017)[102]	Adults with a BMI ≥ 25 kg m^{-2}; nondiabetic; fasting insulin >60 pmol l^{-1}; nonsmokers; free of chronic or acute disease; sample size: n = 41	Double-blind, placebo-controlled, randomized, parallel-arm study	Beverage of strawberry + cranberry polyphenols 333 mg day^{-1} (Tx1) or flavor-matched beverage (Cx1) for six weeks	↑Insulin sensitivity and ↓time of first-phase insulin-secretion response (30 min OGTT) in Tx1
Schell *et al.* (2017)[58]	Adults with BMI > 30 kg m^{-2}, WC > 35 in (females) or >40 in (males), and radiographic evidence of knee OA	Randomized, double-blind, crossover parallel-arm study	Strawberry freeze-dried powder 50 g day^{-1} (~500 g fresh-equivalent) (Tx1); or control powder (Cx1) for 12 weeks	↓Knee pain, serum IL-6, IL-1β, and MMP-3 in Tx1; no effects on fasting glucose
Castro-Acosta *et al.* (2016)[57]	Adults with a BMI of 18–35 kg m^{-2} and otherwise-healthy sample size: n = 23	Randomized, double-blind, four-arm, crossover 2 h postprandial study	High-CHO meals with blackcurrant extract beverage in randomized order: 0, 150, 300, or 600 mg anthocyanins (600 mg extract ~100 g fresh blackcurrants)	↓Postprandial glucose, insulin, GIP, GLP-1 in the 600 mg group
Park *et al.* (2016)[22]	Adults with large WC and any one of the following: FBG: 5.5–6.9 mmol L^{-1}; fasting insulin >75th percentile of 13.13 μIU mL^{-1}; HOMA-IR ≥ 1.0; sample size: n = 25	Single-blinded, four-arm, placebo-controlled, 6 h postprandial study	Breakfast meal with one of four strawberry beverages in a randomized order: 0, 10, 20 or 40 g FDS (10 g FDS ~ 110 g fresh strawberries)	↓Post meal 6-hour insulin after 40 g FDS; pelargonidin-glucuronide inversely related to mean insulin after 20 and 40 g dose ↓Oxidized LDL after 20 g dose
Novotny *et al.* (2015)[60]	Adults with a BMI between 20 and 38 kg m^{-2}; nondiabetic; nonsmokers, fasting TGs < 3.39 mmol L^{-1}; sample size: n = 56	Double-blind, placebo-controlled, parallel-arm study	LCCJ or a flavor/calorie-matched placebo beverage (480 mL day^{-1} for eight weeks)	↓Serum TG, CRP, glucose, insulin resistance, diastolic BP after LCCJ supplementation
Basu *et al.* (2014)[21]	Adult nonsmokers; large WC > 35 inches (females), >40 inches (males) and any two of the following lipid criteria: total-C >200 mg dL^{-1}; LDL-C >100 mg dL^{-1}; TGs > 150 mg dL^{-1}; HDL-C < 50 mg dL^{-1} for women, < 40 mg dL^{-1} for men; not taking lipid lowering medications; sample size: n = 60	Randomized, dose-response controlled study	Low-dose 25 g day^{-1} strawberry powder (Tx1) or low-dose calorie- and fiber-matched control 25 g day^{-1} (Cx1); high-dose 50 g day^{-1} strawberry powder (Tx2) or high-dose calorie- and fiber-matched control (Cx2) for 12 weeks	↓Total- and LDL-C in Tx2 compared with Cx1, Cx2, and Tx1; ↓MDA compared with Cx1 and Cx2 in Tx1 and Tx2; no effects on BG and insulin resistance

Reference (year)	Participants	Study design	Intervention	Significant findings
Lehtonen *et al.* (2011)[62]	Adult females not pregnant; premenopause; BMI: 26–34 kg m^{-2}; total-C 4.5–8 mmol l^{-1}, LDL-C >2.5 mmol l^{-1}, TGs < 4 mmol l^{-1}, BG < 6 mmol l^{-1}, insulin < 25 mU l^{-1}, BP < 160/99 mmHg; non-diabetic and free of chronic diseases; sample size: n = 80	Randomized, crossover, four-arm study	Bilberry 100 g day^{-1} (Tx1); or sea buckthorn dried 100 g day^{-1} fresh-equivalent (Tx2); or sea buckthorn extract 5 g day^{-1} (Tx3); or sea buckthorn oil 5 g day^{-1} (Tx4) for 33–35 days	↓WC from baseline in Tx1 and Tx2; ↓BW in Tx1 from baseline; ↓VCAM in Tx1 and Tx4 ↓ICAM in Tx3
Jin *et al.* (2010)[63]	Adult women not pregnant; premenopause, without chronic disease; BMI including normal weight, overweight and obese; sample size: n = 117	Randomized, double-blind, placebo-controlled parallel-arm study	Fruit + vegetable powder, 6 capsules per day (Tx1); or fruit + vegetable + berry powder, 6 capsules per day (Tx2); or appearance-matched placebo, 6 capsules per day (Cx1) for 60 days	↓MCP-1, MIP-1β, and RANTES; ↑SOD and micronutrients in Tx1 + Tx2; BG and insulin not reported
Stull *et al.* (2010)[19]	Adults with BMI of 32–45 kg m^{-2} and non-diabetic insulin resistance sample size: n = 32	Randomized, double-blind, placebo-controlled parallel-arm study	Freeze-dried whole blueberries 45 g day^{-1} (~2 cups fresh-equivalent) (Tx1); or calorie-matched control beverage (Cx1) for 6 weeks	↑Insulin sensitivity (determined by exogenous glucose infusion divided by fat-free mass) in Tx1

AUC: Area under the curve, BG: blood glucose, BMI: body mass index, BP: blood pressure, C: cholesterol, CRP: C-reactive protein, Cx: control group, FBG: fasting blood glucose, FDS: freeze-dried strawberries, FPG: fasting plasma glucose, GIP: gastric inhibitory polypeptide, GLP: glucagon-like peptide, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, IL: interleukin, LCCJ: low carbohydrate cranberry juice, LDL: low-density lipoprotein, MCP: monocyte chemotactic protein, MDA: malondialdehyde, MIP: macrophage inflammatory protein, MMP: matrix metalloproteinase, OGTT: oral glucose tolerance test, RANTES: Regulated upon Activation, Normal T cell Expressed and Secreted, SOD: superoxide dismutase, TG: triglycerides, Tx: treatment group, WC: waist circumference.

Table 3

Clinical studies on the effects of dietary berry intervention (fresh or processed whole berries and juice) on glycemic control in adults with metabolic syndrome or pre-diabetes

Reference (year)	Participants	Study design	Intervention	Significant findings
Xiao *et al.* (2019)[77]	Adults with prediabetes and insulin resistance and overweight/obesity sample size: $n = 32$	Randomized, single-blinded, crossover triple-arm postprandial meal study	Breakfast meal with frozen whole red raspberries 250 g (Tx1), 125 g (Tx2), or 0 g (Cx1) for 2h-postprandial study	↓2-Hour insulin AUC in Tx1 and Tx2 ↓Peak insulin, peak glucose, and 2-hour glucose AUC in Tx2 *vs.* Cx1 ↓TGs in Tx1 *vs.* Tx2
Espinosa-Moncada *et al.* (2018)[74]	Adult females; nonpregnant; nonsmokers; with MetS; sample size: $n = 40$	Randomized, double-blind, placebo-controlled, crossover parallel-arm study	Agraz (*Vaccinium meridionale* Swartz, Colombian blueberry) berry nectar 200 mL day^{-1} (Tx1); or polyphenol-free macronutrient and taste-matched placebo 200 mL day^{-1} (Cx1) for 12 weeks	↓hsCRP, DNA oxidative damage and ↑antioxidant capacity in Tx1 *vs.* Cx1; no effects on markers of insulin resistance and BG
Kim *et al.* (2018)[73]	Adults with MetS; sample size: $n = 37$	Randomized, double-blind, placebo-controlled, parallel-arm study	Acai berry beverage 325 mL day^{-1} (Tx1); or flavor-matched placebo beverage (Cx1) for 12 weeks	↓IFN-γ and 8-isoprostane in Tx1; no effects on markers of insulin resistance and BG
Hanhineva *et al.* (2014)[103]	Adults with MetS; sample size: $n = 106$	Randomized, triple-arm study	Dietary intervention including 300 g day^{-1} bilberries (Tx1); or healthy diet without berries (Tx2); or control diet (Cx1) for 12 weeks	↓Glucuronidated alk(en)ylresorcinols; ↑plasma HA in Tx1 and Tx2 *vs.* Cx1; no effects on markers of insulin resistance and BG
Simão *et al.* (2013)[71]	Adults with MetS; sample size: $n = 56$	Placebo-controlled, parallel-arm study	Cranberry juice 0.7 L day^{-1} (Tx1); or control group on typical diet (Cx1) for 60 days	↑Adiponectin, folic acid ↓Lipoperoxidation and protein oxidation; homocysteine with Tx1 *vs.* Cx1; no effects on insulin resistance and BG
Puupponen-Pimia *et al.* (2013)[53]	Adults with a BMI 26–39 kg m^{-2} with features of MetS; sample size: $n = 32$	Randomized, controlled, parallel-arm study	Strawberry puree 100 g day^{-1} + raspberries 100 g day^{-1} + cloudberries 100 g day^{-1} (Tx1); or berry-free control group (Cx1) for 16 weeks	↑Leptin concentration in Tx1; serum lipidomics revealed 20 discriminating lipids in Tx1 *vs.* Cx1; BG and insulin not reported
Basu *et al.* (2011)[70]	Adults with MetS; sample size: $n = 36$	Randomized, double-blind, placebo-controlled, parallel-arm study	Cranberry juice 480 mL day^{-1} (Tx1); or energy and flavor-matched placebo beverage (Cx1) for eight weeks	↑Plasma antioxidant capacity and ↓oxidized LDL and malondialdehyde in Tx1 *vs.* Cx1; no effects on BG
De Mello *et al.* (2011)[72]	Adults with features of MetS and impaired glucose control sample size: $n = 104$	Randomized, placebo-controlled, parallel-arm study	Healthy diet with whole-grain replacement, fatty fish, and bilberries totaling 300 g day^{-1} fresh-equivalent (Tx1); or diet with whole-grain replacement only and unchanged fish & berry consumption (Tx2); or unchanged diet with avoidance of whole-grain products and berries and limited fatty fish intake (Cx1) for 12 weeks	↓plasma E-selectin in Tx1 only ↓plasma hsCRP in Tx1 and Tx2
Basu *et al.* (2010)[20]	Adults with MetS; sample size: $n = 48$	Randomized, placebo-controlled parallel-arm study	Blueberries 350 g day^{-1} fresh-equivalent (Tx1); or water control (Cx1) for eight weeks	↓Systolic and diastolic BP, ox-LDL, MDA, HNE in Tx1 *vs.* Cx1; no effects on BG and insulin resistance
Basu *et al.* (2010)[65]	Adults with MetS; sample size: $n = 27$	Randomized, placebo-controlled, parallel-arm study	Strawberry, freeze-dried powder 50 g day^{-1} (~3 cups fresh-equivalent) (Tx1); or water control (Cx1) for eight weeks	↓Total- & LDL-C, small LDL particles, and plasma VCAM-1 in Tx1 *vs.* Cx1; no effects on BG

AUC: Area under the curve, BG: blood glucose, BP: blood pressure, C: cholesterol, Cx: control group, HA: hippuric acid, HNE: hydroxynonenal, hsCRP: high-sensitivity C-reactive protein, IFN: interferon, LDL: low-density lipoprotein, MDA: malondialdehyde, MetS: Metabolic Syndrome, TG: triglycerides, Tx: treatment group, VCAM: vascular cell adhesion protein.

Table 4

Clinical studies on the effects of dietary berry intervention in adults with T2D

Reference (year)	Participants	Study design	Intervention	Significant findings
Schell *et al.* (2019)[83]	Adults with T2D on medications sample size: $n = 25$	Randomized, 2- phase crossover study	Phase 1: Postprandial response (4 h) to raspberry supplementation (Tx1); or control meal (Cx1)	↓2-Hour and 4-hour BG in Tx1 *vs.* Cx1
			Phase 2: Raspberry supplementation (Tx2) or controlled diet without raspberries (Cx1) followed by 2-week washout; for 10 weeks	↓4-Hour IL-6 and hsTNF-α in Tx1 *vs.* Cx1 ↓IL-6 and hsTNF-α in Tx2 *vs.* Cx2
Lazavi *et al.* (2018)[88]	Adults with T2D on medications sample size: $n = 42$	Randomized, controlled, parallel-arm study	Barberry juice 200 mL day^{-1} (Tx1); or non-intervention group (Cx1) for eight weeks	↓SBP, DBP, FBG, total cholesterol, and triglycerides in Tx1 ↑Paraoxonase-1 in Tx1 vs. Cx1
Schell *et al.* (2017)[104]	Adults with T2D and WC > 89 cm (females) or >102 cm (males) on medications sample size: $n = 25$	Randomized, crossover parallel-arm postprandial (4 h) study	High-fat fast-food-style breakfast (70 g fat, 974 kcal) with dried cranberries 40 g (Tx1) or banana 80 g (Cx1)	↓2-Hour and 4-hour glucose in Tx1
Yang *et al.* (2017)[85]	Adults with prediabetes or early untreated T2D sample size: $n = 138$	Randomized, double-blind, placebo-controlled, parallel-arm study	Anthocyanin capsules (bilberry & black currant) 320 mg day^{-1} (Tx1); or placebo-capsule (Cx1) for 12 weeks	↓HbA_{1C}, LCL-c, apo A_1, apo B in Tx1 *vs.* Cx1
Cai *et al.* (2015)[89]	Adults with T2D on medications sample size: $n = 67$	Randomized, controlled, parallel-arm study	Goji berry capsule 300 mg day^{-1} (Tx1); or placebo capsule (Cx1) for 3 months	↓BG and ↑OMTT insulinogenic index and HDLs in Tx1
Moazen *et al.* (2013)[84]	Adults with T2D, nonsmokers, not on medications sample size: $n = 36$	Randomized, double-blind, placebo-controlled study	Strawberries freeze-dried ~500 g day^{-1} fresh-equivalent (Tx1); or flavor- and macronutrient-matched placebo powder (Cx1) for six weeks	↓CRP, MDA from baseline in Tx1 ↓HbA_{1C} and ↑total antioxidants with control in Tx1
Shidfar *et al.* (2012)[82]	Adult males with T2D sample size: $n = 58$	Randomized, double-blind, placebo-controlled, parallel-arm study	Cranberry juice drink 1 cup per day (Tx1); or placebo (Cx1) for 12 weeks	↓BG and apolipoprotein B in Tx1 *vs.* Cx1 and baseline ↑Apolipoprotein A1 and paraoxonase-1 activity in Tx1 *vs.* Cx1 and baseline
Wilson *et al.* (2010)[81]	Adults with T2D on medications sample size: $n = 13$	Randomized, single-crossover postprandial (2 h) study	Raw cranberry 55 g (Tx1); or sweetened dried cranberries 40 g (Tx2); or reduced-sugar dried cranberries 40 g (Tx3); or white bread 57 g (Tx4)	↑BG elevation persistence in Tx4 *vs.* other Tx groups ↓ 60 min plasma insulin in Tx3 *vs.* Tx2 and Tx4 ↓Insulin AUC Tx1 and Tx3 *vs.* Tx2 and Tx4

Abbreviations: apo: apolipoprotein, AUC: area under the curve, BP: blood pressure, CRP: C-reactive protein, Cx: control group, DBP: diastolic blood pressure; DM: diabetes mellitus, FBG: fasting blood glucose; FDS: freeze-dried strawberries, HbA_{1C}: glycated hemoglobin, HDL: high-density lipoprotein, hsTNF: high-sensitivity tumor necrosis factor, IL: interleukin, MDA: malondialdehyde, SBP: systolic blood pressure; Tx: treatment group, OMTT: oral metabolic tolerance test, WC: waist circumference.

Table 5

Clinical studies on the effects of dietary supplements of berry extracts in adults with cardio-metabolic risks

Reference (year)	Participants	Study design	Intervention	Significant findings
Xie *et al.* (2017)[105]	Healthy adults, former smokers with 6 month cessation sample size: $n = 49$	Randomized, placebo-controlled trial	Aronia extract 500 mg day^{-1} (Tx1); or color-matched placebo (Cx1) with low-polyphenol diet for 12 weeks	↓LDL-C, total cholesterol, and LCL-receptor protein in Tx1 *vs.* Cx1
Alvarado *et al.* (2016)[91]	Pre-diabetic adults sample size: $n = 31$	Pre-post intervention trial	Macqui berry extract (Delphinol®) 150 mg day^{-1} (Tx1) for three months	↓HbA_{1C}, LDL and ↑HDL from baseline in Tx1
Alvarado *et al.* (2016)[92]	Pre-diabetic adults sample size: $n = 43$	Exploratory placebo-controlled, crossover, acute-dose response (2 h) study	Macqui berry extract (Delphinol®) 0 mg (Cx1), 60 mg (Tx1), 120 mg (Tx2), and 180 mg (Tx3) paired with 75 g glucose-solution OGTT	↓BG and insulin in Tx groups
An *et al.* (2016)[90]	Pre-diabetic adults sample size: $n = 44$	Randomized, double-blind, placebo-controlled, triple-arm study	Black raspberry extract 0 mg day^{-1} (Cx1), 900 mg day^{-1} (Tx1), and 1800 mg day^{-1} (Tx2) for 12 weeks	↓AUC for glucose (2 h- OGTT) in Tx2 *vs.* Cx1 ↓Monocyte chemoattractant protein-1 and oxidized LDL in Tx groups
Davinelli *et al.* (2015)[106]	Adults with BMI 25–30 kg m^{-2}, light smokers (< 1 pack per day) sample size: $n = 42$	Randomized, double-blind, placebo-controlled, parallel-arm study	Macqui berry extract (Delphinol®) 450 mg day^{-1} (Tx1); or placebo (Cx1) for four weeks	↓Oxidized LDL in Tx1 from baseline ↓Urinary 8-iso-prostaglandin F2a in Tx1 at four weeks
Li *et al.* (2015)[93]	Adults with T2D on medications sample size: $n = 58$	Randomized, double-blind, placebo-controlled, parallel-arm study	Anthocyanin extract from bilberry and blackcurrant (Medox) 320 mg day^{-1} (Tx1); or placebo (Cx1) for 24 weeks	↓BG, insulin resistance, LDL, triglycerides, apolipoprotein B-48, apolipoprotein C-III, 8-iso-prostaglandin F2a, 13-hydroxyoctadecadienoic acid, and carbonylated proteins in Tx1 *vs.* Cx1 ↑adiponectin, β-hydroxybutyrate, and HDL in Tx1 *vs.* Cx1
Hidalgo *et al.* (2014)[97]	Adults with BG < 100 mg dL^{-1} and/or IGT 100–125 mg dL^{-1} with BMI < 30 kg m^{-2} sample size: $n = 10$	Randomized, double-blind, placebo-controlled, crossover acute-dose (2 h) response study	Macqui berry extract (Delphinol®) 0 mg (Cx1), 200 mg (Tx1) paired with 75 g boiled rice OGTT	↓BG and insulin in Tx1 *vs.* Cx1
Lee *et al.* (2008)[96]	Adults with T2D on medications sample size: $n = 30$	Randomized, double-blind, placebo-controlled parallel-arm study	Encapsulated cranberry extract powder 1500 mg day^{-1} (Tx1); or placebo capsules (Cx1) for 12 weeks	↓LDL, HDL, total cholesterol in Tx1 *vs.* baseline and Cx1

Abbreviations: AUC: area under the curve; BG: blood glucose; BMI: body mass index; Cx: control group; DM: diabetes mellitus; HbA_{1C}: glycated hemoglobin; HDL: high-density lipoprotein; HTN: hypertension; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; LDL: low-density lipoprotein; OGTT: oral glucose tolerance test; SBP: systolic blood pressure; Tx: treatment group.