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REVIEW

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Cardiovascular disease protective properties of blueberry polyphenols (*Vaccinium corymbosum*): a concise review

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Abstract

Increasing epidemiological evidence suggests inverse association between consumption of diets rich in fruits and vegetables and the incidence of cardiovascular diseases (CVD), metabolic syndrome disorders, certain types of cancer, neurodegenerative disorders, and other forms of human chronic diseases. This may be due to the contents of some bioactive phytochemicals, especially polyphenols, which are abundant in fruits and vegetables and have antioxidant effects. Berry fruits are reported to have the highest total antioxidant capacity (TAC) among fruits. They may protect against CVD and hypertension either directly or in tandem with other cellular mechanisms. Blueberry anthocyanins have been reported to exhibit cardiovascular protective health effects by preventing cholesterol-induced atherosclerosis, and reduction of oxidative and inflammatory damages to the endothelium through several mechanisms. Such mechanisms may involve suppressing the release of inflammatory mediators, protection against ischemic damage of the heart as well as cardiomyocyte survival, lower systolic and mean arterial pressures and renal nitrite content in addition to multiple other beneficial effects. However, several limitations in existing studies make it difficult to draw conclusions regarding the preventive effects of blueberries and other polyphenols-rich foods, especially as data supporting a causal relationship between direct antioxidant capacity and CVD are insufficient or limited. It is also unclear, which molecules exert this effect since few studies with isolated polyphenols have been conducted in addition to a lack of proper understanding of other mechanisms that may be involved. This review is, therefore aimed at discussing some of the current literature information on the cardiovascular protective effects of blueberries with suggestions for future research directions.

Keywords Bioactivity, Antioxidant capacity, Hypertension, Inflammation, Atherosclerosis, Oxidative stress, Phytochemicals

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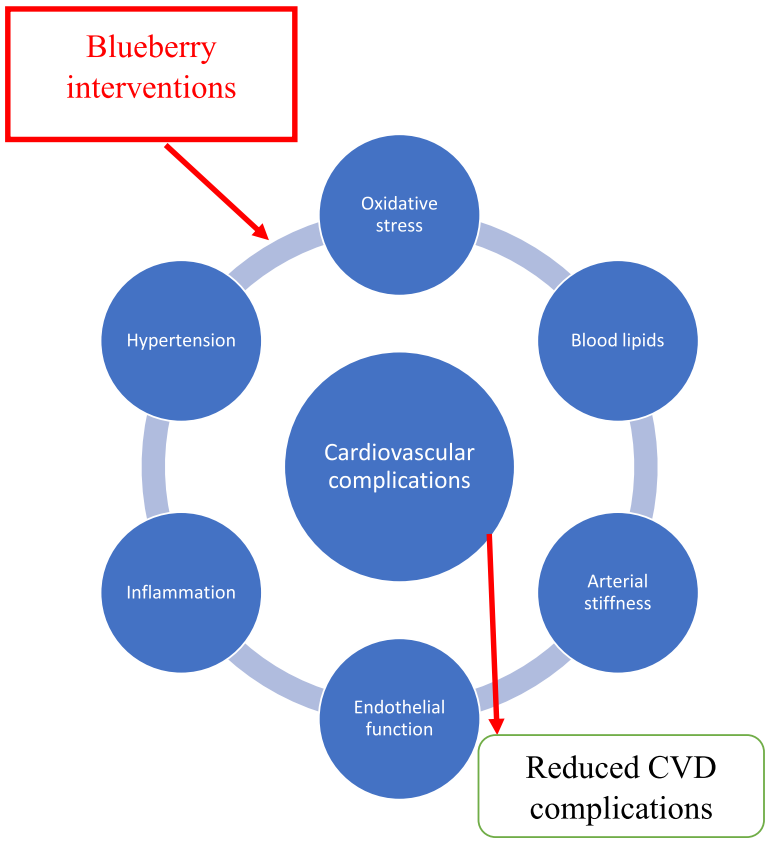
Graphical Abstract

Graphical abstract demonstrating the overall mechanisms of CVD protection by blueberry and blueberry polyphenols and anthocyanins. Blueberry consumption leads to reduced CVD complications due to the modulation of several mechanisms associated with CVD.



Introduction

There has been growing epidemiological and clinical evidences to suggest that consumption of diets rich in fruits and vegetables leads to a reduction in the incidence of certain diseases such as cardiovascular disease (CVD), metabolic syndrome disorders, certain types of cancer, and neurodegenerative disorders (Basu, Du, et al. 2010; Habauzit & Morand 2012; Hollman et al. 2011; Routray & Orsat 2011). For instance, berry fruits have long been known for their cardiovascular health benefits (Basu & Lyons 2012; Curtis et al. 2019; Curtis et al. 2022; Olas 2018; Pap et al. 2021). This may be due to their contents of some bioactive phytochemicals and polyphenols which have antioxidant effects (Andriantsitohaina et al. 2012; Curtis et al. 2019; Johnson et al. 2015; Johnson et al. 2017). Berry fruits, including blueberry are known to exhibit the highest total antioxidant capacities (TAC) among fruits. They could therefore, protect against CVD and hypertension either directly or in association with other mechanisms such as modification of enzymes systems and cell signaling (Basu, Du, et al. 2010; Basu & Lyons 2012; Wolfe et al. 2008; Yang et al. 2011). Also, results from several observational and human intervention studies support a protective relationship between the consumption of polyphenol rich foods and chronic diseases, especially CVD (Curtis et al. 2019; Del Bo et al. 2022; Hollman et al. 2011; Kalt et al. 2020; Wu et al. 2018).

CVD is one of the leading causes of death worldwide with an enormous health burden, especially in the US where it is estimated to affect about 83 million adults (Del Bo et al. 2022; Erdmann et al. 2008; Habauzit & Morand 2012; Shaughnessy et al. 2009; Stull et al. 2015). There are many CVDs but the common types of CVDs are coronary heart disease (CHD), hypertension or high blood pressure (HBP), Congestive heart failure (CHF), cardiac arrest (heart attack), and cardiac arrythmia.

Others are peripheral artery disease (PAD), stroke, congenital heart failure (CHF), cardiomyopathy, pericardial disease, rheumatic heart disease (RHD) and vascular disease. The risk factors of CVD are very varied and includes obesity, hypertension, hyperglycemia and high blood lipoproteins that may be prone to atherogenesis (Wang et al. 2022; Xu et al. 2021). Though the causes of CVD are multifactorial, oxidative damage to biomolecules such as proteins, lipids, and DNA, which progresses with ageing is considered a major contributor (Del Bo et al. 2022; Habauzit & Morand 2012; Hollman et al. 2011; Shaughnessy et al. 2009). This leads to atherogenesis resulting in the obstruction of arterial lumen and inflammation of the arteries (Ames et al. 1993; Hollman et al. 2011; Stull et al. 2015; Wang et al. 2022). This is further characterized by the oxidation of low-density lipoprotein (LDL) cholesterol and the accumulation of oxidized LDL (ox-LDL) in macrophages leading to the formation of foam cells and the production of lipid peroxidation products, which contribute to further plaque formation and growth (Habauzit & Morand 2012; Hollman et al. 2011; Leopold & Loscalzo 2009; Wang et al. 2022). These may also lead to additional complications such as vasoconstriction that may result in cessation of blood flow and accompanying clinical events (Habauzit & Morand 2012; Stull et al. 2015; Wu et al. 2018) as shown in Fig. 1.

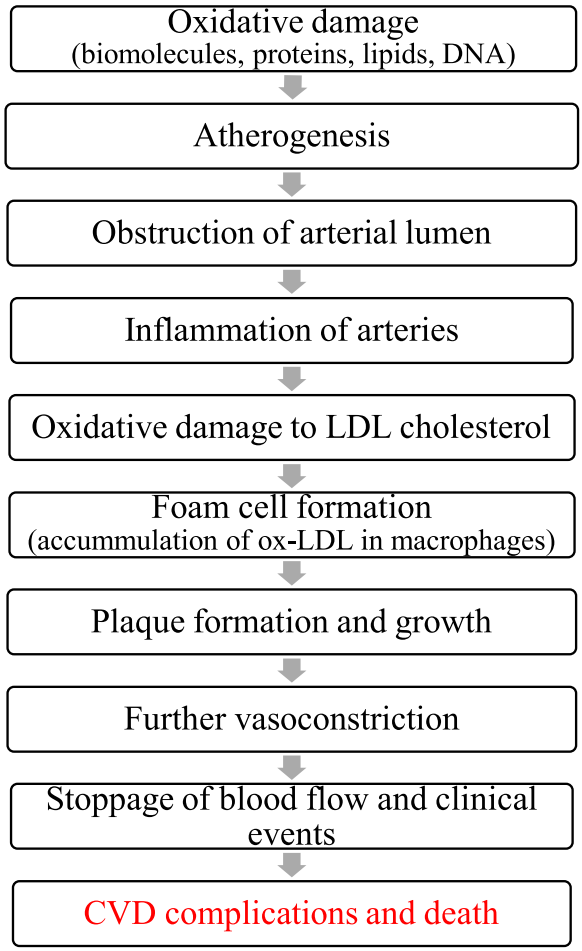


Fig. 1 Pathophysiology of oxidative damage induced cardiovascular disease (CVD) complications and death. DNA (deoxyribonucleic acid), LDL (low density lipoprotein), ox-LDL (oxidized low-density lipoprotein), CVD (cardiovascular disease)

Antioxidant protective effects of fruits and vegetables had initially been attributed to the presence of vitamins and carotenoids, but more recent works have focused increased attention on polyphenols. However, results are inconclusive due to their structural diversity, wide distribution in foods and limitations in experimental studies (Del Bo et al. 2022; Del Rio et al. 2013; Habauzit & Morand 2012; Johnson et al. 2017). Therefore, to ascertain the efficacy of polyphenols requires a properly designed human intervention trial (Curtis et al. 2022; Del Rio et al. 2013; Johnson et al. 2017; Wood et al. 2019). A number of short-term, small-scale human intervention studies have tested the effect of polyphenol-rich foods, especially those containing blueberry polyphenols, on well-recognized, medically significant biomarkers for CVD, including hypertension, endothelial dysfunction, lipid metabolism, and platelet activation as will be discussed in relevant sections later (Curtis et al. 2022; Del Rio et al. 2013; Habauzit & Morand 2012; Pandey & Rizvi2009; Stull et al. 2015).

Blueberry is one of the most popular fruits consumed in North America, has high levels of anthocyanin, a major polyphenolic group of compounds that are well recognized for their nutritional and beneficial health effects (Ahmet et al. 2009; Basu, Du, et al. 2010; Basu & Lyons 2012; Routray & Orsat 2011; Shaughnessy et al. 2009). Blueberry polyphenols are reported to possess antidiabetic, antibacterial, and anticarcinogenic properties and as such, along with its products have found wide use among the populace (Johnson et al. 2017; Kalt et al. 2020; Routray & Orsat 2011; Stull et al. 2015). They are reported to have one of the highest TAC of all fruits known to date, containing polyphenols such as anthocyanins, phenolic acids, tannins and flavanols (Elks et al. 2011; Johnson et al. 2017; Olas 2018). Blueberry anthocyanins have been reported to have cardiovascular protective health effect by preventing cholesterol-induced atherosclerosis (Basu, Du, et al. 2010; Del Bo et al. 2022; Kraft et al. 2005; Stull et al. 2015; Wu et al. 2018), as well as reduction of oxidative and inflammatory damage to the endothelium by suppressing the release of inflammatory mediators (Curtis et al. 2022; Del Bo et al. 2022; Youdim et al. 2002). They also have protection against ischemic damage of the

heart as well as cardiomyocyte survival (Ahmet et al. 2009), lower systolic and mean arterial pressures and renal nitrite content (Shaughnessy et al. 2009), attenuate and even improve age-related behavioral and neuronal deficits in rodents (Elks et al. 2011) and a host of other beneficial actions (Routray & Orsat 2011).

However, several limitations in existing studies made it difficult to draw conclusions regarding the preventive effects of blueberries and other polyphenols-rich foods. Data supporting a causal relation between direct antioxidant capacity and CVD are insufficient or limited. It is also unclear, which molecules exert these beneficial effects because few studies with isolated polyphenols have been conducted. Therefore, several potential polyphenolic compounds remain uninvestigated. There is also a lack of proper understanding of other mechanisms that may be involved. This review is therefore, aimed at discussing some of the published reports on the cardiovascular protective effects of blueberries and suggest future research directions in this field. It is suggested that an understanding of the role of gut microbiota in enhancing polyphenol bioavailability and the application of metabolomics profiling will assist in elucidating the metabolite changes associated with blueberry consumption that may have effects on cardiovascular health modulation.

Methodology and data collection

With a comprehensive search of the PubMed database, published articles on cardiovascular protection of blueberry polyphenols were collected. Additional data searches were done using other online platforms. Reference citations were done using the EndNote Version 9, making use of trusted sources such as PubMed, NCBI, Web of Science, Science Direct, Google Scholar and other trusted journals. These literature searches were also done using the keywords "bioactivity", "cardiovascular", "antioxidant capacity", "blueberry", "hypertension", and "polyphenols". Specifically, the main focus was to include recently published clinical studies that will highlight new knowledge on the CVD protective effects of blueberry polyphenols, especially, as reported in the last 10 years as much as is possible. Firstly, a general overview of CVD was given, followed by the bioactivities of blueberry polyphenols, the various mechanisms of action by which blueberry polyphenols exhibit CVD protection and finally, an overview of the limitations, challenges, and future perspectives.

Bioactivity of blueberry polyphenols

Blueberry polyphenols comprise anthocyanins, proanthocyanidins, phenolic acids and flavanols, with anthocyanins (flavonoids) being mainly responsible for the antioxidant and bioactive properties, accounting for approximately 35–74% of the total phenolic compounds, in addition to the hydroxycinnamic acid derivates, flavonols and flavan-3-ols as shown in Table 1 (Basu & Lyons 2012; Elks et al. 2011; Tobar-Bolaños et al. 2021). Consequently, blueberry and its products have found wide applications in different foods. They are consumed as fresh and frozen fruits, and as ingredients in baked products, fruits fillings, in muffins, canned products, preserves, syrups, juices, beverages, food colors, and yoghurts (as prebiotics) and in beverages (Routray & Orsat 2011; Tobar-Bolaños et al. 2021). Blueberries have been reported to be promising functional food and nutraceutical ingredients with respect to their beneficial effects on vascular health, partly due to the inhibitory ability of the activity of their circulating polyphenolic metabolites against NADPH oxidase, which consequently enhance nitric oxide bioavailability along with improved endothelial-dependent vasodilation (Basu, Du, et al. 2010; Del Bo et al. 2022; Johnson et al. 2015; Kalt et al. 2020; Rodriguez-Mateos et al. 2013).

The antioxidant activity of foods with high polyphenolic contents has been a subject of interest to researchers (Blacker et al. 2013; Wu et al. 2018). The presence of phenolic hydroxyl groups (which is common to all polyphenols) has been reported to be the basis for this antioxidant activity both in vitro and in vivo (Blacker et al. 2013; Hollman et al. 2011). The phenolic content in blueberry is reported to be on average 412 mg gallic acid equivalents/100 g fresh weight, with significantly higher antioxidant capacity than vitamin C or vitamin E, though the extent to which in vitro antioxidant capacities can be translated into in vivo effects, especially postprandial protection is still not fully understood (Blacker et al. 2013; Fernandez-Panchon et al. 2008). One of the major reasons for this disconnect between in vitro and in vivo data may be due to poor absorption and availability of fruit polyphenolic compounds, necessitating more elaborate in vivo studies, focusing on metabolite profiles that will establish consensus between in vitro and in vivo outcomes (Blacker et al. 2013). Additionally, evidence of the impacts of polyphenols-rich products on biomarkers of oxidative stress in humans is limited (Curtis et al. 2022; Habauzit & Morand 2012; Hollman et al. 2011). It is, therefore vital to also look beyond the direct antioxidant action of polyphenols and focus on other mechanisms such as molecular signaling pathways and regulation of cellular processes such as inflammation, regulation of flow-mediated dilatation (FMD) in addition to using metabolomics profiling approach (Gonzalez et al. 2011; Sies 2010; Wood et al. 2019).

Table 1 The concentration of total phenolic compounds and anthocyanins in different berries and their products

Berries	Phenolic compounds (mg/100 g)	Anthocyanins (mg/100 g)	References
Aronia (*Aronia melanocarpa*) fruits	2080	240	Olas (2018)
Blueberry (*Vaccinium corymbosum*) fruits	30.81	92.32	Serafini et al. (2009)
Blueberry (*Vaccinium corymbosum L* "Puru")	392.78 ± 34.70	50.60 ± 11.77	Rossi et al. (2022)
Blueberry (*Vaccinium corymbosum L* "Friendship")	1561.46 ± 41.61	281.56 ± 25.95	Rossi et al. (2022)
Strawberries (*Fragaria annassa*) fruits	225	60–80 g per 100 g	Olas (2018)
Blueberry (*Vaccinium corymbosum*) freeze-dried powder	1624	742	Basu et al. (2010b)
Blueberries (*Vaccinium corymbosum L* "Brigitta")	242.4 ± 23.9	116.1 ± 6.9	Del Bo et al. (2013)
Blueberry (*Vaccinium corymbosum*)	773.6	290.3	Stull et al. (2015)
Blueberry (*Vaccinium corymbosum*) freeze-dried powder	844.58	469.48	Johnson et al. (2015)
Blueberry (*Vaccinium corymbosum*) freeze-dried powder	765.6	261.8	Stote et al. (2020)
Blueberry (*Vaccinium corymbosum*) drink	692 ± 13	339 ± 6.1	Rodriguez-Mateos et al. (2014b)
Blueberry (*Vaccinium corymbosum*) bun	637 ± 28	196 ± 7.7	Rodriguez-Mateos et al. (2014b)
Blueberry (Highbush)	–	387	Kalt et al. (2020)
Blueberry (Lowbush)	–	487	Kalt et al. (2020)
Cherry (Sweet)	–	122	Kalt et al. (2020)
Raspberry (Red)	–	92	Kalt et al. (2020)
Blueberry (*Vaccinium corymbosum*) mixture of different varieties	1906.6 ± 432.4	1312.5 ± 297.9	Giongo et al. (2011)
Wild blueberry juice	2138	314	Stote et al. (2017)
Cranberries (*Vaccinium macrocarpon*) fruits	120–315	–	Olas (2018)
Grape (*Vitis vinifera*) seed extract	500	–	Olas (2018)
Raspberries (*Rubus idaeus*)	126 mg/100 g fruits		Olas (2018)
Sea buckthorn (*Elaeagnus rhamnoides L.*) berries	260–490 mg/100 g FW	–	Olas (2018)
Cranberry (*Vaccinium oxycoccus, Vaccinium macrocarpon*)	392.37	3.60	Pap et al. (2021)
Blueberry fruits (mean values across all varieties)	883.5	163.38	Rossi et al. (2022)

Oxidative stress and chronic inflammation are known factors responsible for the pathogenesis and perpetuation of hypertension, which consequently serves as a major risk factor for several chronic diseases such as CVD, cerebrovascular diseases, renal diseases, type-2 diabetes, and cancer (Johnson et al. 2017; Kalt et al. 2020; Ono-Moore et al. 2016). Therefore, interventions especially with blueberries containing high bioactive polyphenolic and other compounds that protect against oxidative stress and inflammation could be an effective approach to reducing chronic diseases such as CVD (Johnson et al. 2017; Kris-Etherton et al. 2002; Liu 2003; Liu et al. 2015).

There are several studies conducted on the beneficial and nutritional aspects of blueberries which relate to whole blueberries or blueberry juices while a few were on blueberry extracts (Basu, Du, et al. 2010; Basu & Lyons 2012; Routray & Orsat 2011). Blueberry anthocyanins have been reported to exhibit many beneficial effects beyond their antioxidant property, for instance, several mechanistic studies have suggested the possible bioactivities of blueberry polyphenols to include antihypertensive, antioxidative, antidiabetic, anti-obesity, anti-inflammatory, antihyperlipidemic and anticholesterolemic activities (Ahmet et al. 2009; Basu, Du, et al. 2010; Basu & Lyons 2012; Curtis et al. 2022; Elks et al. 2011; Shaughnessy et al. 2009; Youdim et al. 2002). These activities may have positive impacts on the cardiovascular health of the individuals either directly or indirectly (Basu, Du, et al. 2010; Curtis et al. 2022; Liu et al. 2015). Blueberry anthocyanins have been reported to be positively associated with improvements in biomarkers of cardiovascular endpoints and metabolic syndromes as well as numerous other beneficial effects (Curtis et al. 2019; Del Bo et al. 2022; Kalt et al. 2020; Wood et al. 2019). Additionally, daily blueberry consumption has been shown to improve endothelial function in subjects with metabolic syndrome (Stull et al. 2015). Endothelial dysfunction is one of the early steps in the atherosclerotic process with great adverse consequence of CVD outcomes (Stull et al. 2015; Yeboah et al. 2007). The improvements in endothelial dysfunction are mainly due to the reduction in the risk factors for CVD that are associated with vascular abnormalities (Golovinskaia & Wang 2021; Stull et al. 2015). Some of the possible mechanisms of CVD protection by blueberries and blueberry polyphenols and anthocyanins are shown in Fig. 2.

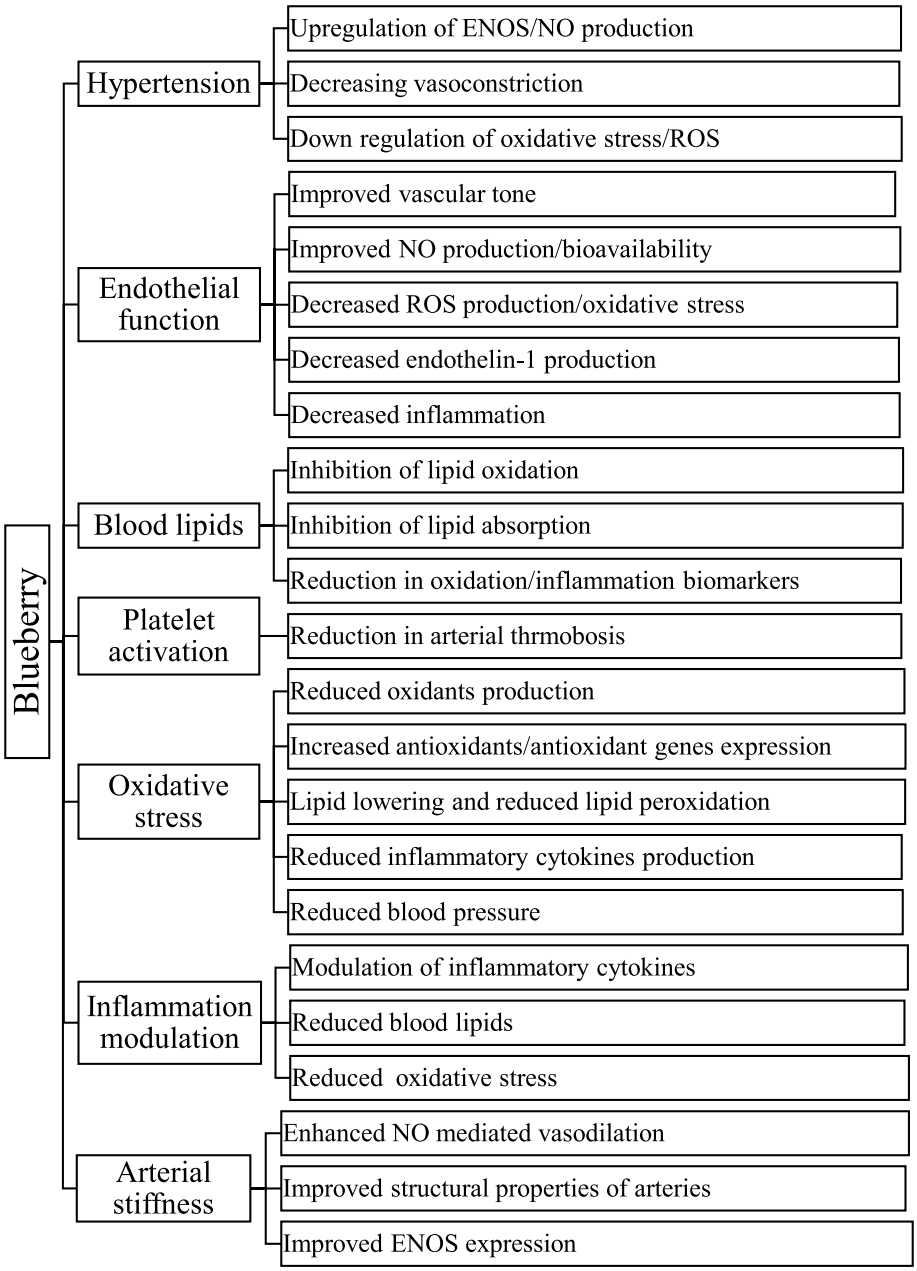


Fig. 2 Mechanisms of CVD protection by blueberry and blueberry polyphenols and anthocyanins. ENOS (endothelial nitric oxide synthase), NO (nitric oxide), ROS (reactive oxygen species)

Cardiovascular protective benefits of whole blueberries and blueberry polyphenols

According to Hollman et al. (2011), several studies support the association between the consumption of foods rich in polyphenols and CVD protective effect, reduced overall mortality or reduced risk of CVD. Most of the human studies done to establish these CVD protective effects of fruits, berries and blueberries are however, reported to be flawed as sometimes they lack proper controls, relevant study population, and also do not provide a detailed compositional analysis of the foods that were tested (Del Rio et al. 2013). For example, some of the studies used polyphenol-rich foods while a few used extracts or isolated polyphenolic compounds. Consequently, it remains largely unknown if the observed effects could be attributed to the polyphenols or other compounds present in the foods (Habauzit & Morand 2012). Ascertaining whether or not polyphenols, and in

particular, blueberry polyphenols are responsible for the observed effects requires a properly designed human clinical intervention study (Curtis et al. 2022; Del Bo et al. 2022; Del Rio et al. 2013). Some of the studies conducted to test the effect of blueberry polyphenols on biomarkers for CVD, including hypertension, endothelial dysfunction, arterial stiffness, oxidative stress, inflammation, lipid metabolism, and platelet activation as discussed in the following section (Table 2).

Blood pressure (BP) lowering ability of blueberries and blueberry polyphenols

Globally, hypertension is a leading risk factor for CVD, stroke, end stage renal disease and premature death (Erdmann et al. 2008; Shaughnessy et al. 2009; Wang et al. 2022). Therefore, lowering of BP using dietary approaches may assist in decreasing end-organ damage associated with hypertension. Available evidence suggests that consuming foods rich in some flavonoids, especially cocoa polyphenols have BP-lowering ability and therefore, offers protection against CVD and stroke (Del Bo et al. 2022; Del Rio et al. 2013; Habauzit & Morand 2012; Moline et al. 2000). Other polyphenol sources such as tea (Hooper et al. 2008), pomegranate (Stowe 2011), berries (Erlund et al. 2008), orange juice (Morand et al. 2011) have been studied with varying degrees of success.

Blueberry supplementation was reported to significantly decrease systolic BP and diastolic BP in pre-hypertensive individuals with metabolic syndrome disorders (Basu, Du, et al. 2010). Forty-eight participants (obese men and women) fed 50 g freeze-dried blueberry powder (equivalent to 350 g fresh blueberry) for 8 weeks had 6 and 4% reductions in systolic BP, and diastolic BP respectively compared to the placebo (1.5 and 1.2%). This BP-lowering ability of blueberry was potentially proposed to be due to the ability of the anthocyanin constituents to ameliorate hypertension through several pathways including upregulating endothelial nitric oxidase synthase, decreasing vasoconstriction through nitric oxide-mediated pathway, and downregulating renal oxidative stress (Basu, Du, et al. 2010). The study concluded that blueberry supplementation could be a potential therapeutic dietary approach to mitigate hypertension and CVD incidence. Similar improvements were obtained in a study involving post-menopausal women for 8 weeks with pre- and stage 1-hypertension, suggesting that regular consumption of blueberry has BP-lowering effects that can be considered to be clinically significant (Johnson et al. 2015).

High BP is also known to cause changes in the endothelium leading to decreased arterial mobility and increased arterial stiffness (Onuh & Qiu 2020; Stull et al. 2015). In a doubled blind, placebo-controlled study to investigate the ability of blueberry to modify BP in 44 adult subjects with metabolic syndrome consuming 45 g of blueberry daily for 6 weeks, it was reported that there were no changes between the blueberry and placebo group although endothelial function was improved (Stull et al. 2015). The lack of effect on BP was attributed to the short duration of the study (6-weeks), suggesting a longer duration may have had a positive outcome on blood pressure. Also, the study participants were reported to be using antihypertensive drugs, which was one of the inclusion criteria and may be a confounding factor.

Improvement in endothelial functions by blueberries and blueberry polyphenols

Endothelium function is a well-known surrogate marker for vascular health as it regulates the vascular tone, adhesion of leucocytes, platelet activity and thrombosis (Del Bo et al. 2022; Del Rio et al. 2013; Habauzit & Morand 2012; Stull et al. 2015). Endothelial dysfunction is one of the initial steps in the development of atherosclerosis, which leads to increased incidences of adverse CVD outcomes (Stull et al. 2015; Wang et al. 2022). It is a measure of the changes in both the vascular tone and endothelium-derived substances that control vascular tone, blood flow, vasodilation, and vasoconstriction (Johnson et al. 2015). Several studies suggest that consumption of flavonoids-rich foods improves endothelial function in CVD patients as well as healthy volunteers (Del Rio et al. 2013; Habauzit & Morand 2012; Hooper et al. 2008; Stull et al. 2015). Flavan-3-ol-rich cocoa has previously been reported to improve endothelium dependent vasodilation by increasing the availability of nitric oxide (NO) in individuals (Del Rio et al. 2013; Habauzit & Morand 2012; Hooper et al. 2008). Wine resveratrol, black tea, grape, and pure polyphenolic compounds such as epicatechin, quercetin and hesperidin were reported to exhibit similar beneficial effects (Habauzit & Morand 2012; Hooper et al. 2008; Morand et al. 2011).

In a study of 42 adult participants with metabolic syndrome distributed between a blueberry arm and a placebo arm consuming 45 g of either blueberry or the placebo for 6 weeks, it was discovered that the endothelial function was significantly improved from baseline to end of trial and that this improvement occurred irrespective of the lack of effect on BP (Stull et al. 2015). The mean change in resting endothelial function, expressed as reactive hyperemia index (RHI) after adjusting for confounding factors (percent body fat and gender) was reported to have greater improvement in the blueberry group compared to the placebo (0.32 ± 0.13 compared to -0.33 ± 0.14). This outcome was reported to confirm previous studies on blueberry consumption and improvement in endothelial function (Rodriguez-Mateos et al.

Table 2 Summary of human studies on the CVD protective effects of blueberries

S/N	Interventions	Subjects/size	Dose	Study duration	Main findings	References
1.	Randomized, control, cross-over dietary intervention trial	A group of 20 men and women aged ≥60 years	250 mg blueberry mousse containing at least 300 mg anthocyanins versus control drink containing fructose, glucose and blueberry saccharose.	One (1) day intervention separated by 1-week washout.	1. Reported protocols on vascular function, oxidative stress, and inflammation.	Del Bo et al. 2022
2.	A parallel, double-blind randomized clinical intervention trial	Forty-five (45) adult men with metabolic syndromes	26 g (freeze-dried) blueberries (1 cup/150 g fresh blueberries)	24 hours acute intervention	1. Improved postprandial levels of glucose, insulin, total cholesterol, HDL-C, L-HDL-P, XL-HDL-P and Apo-A1 but not LDL-C, TG, or Apo-B. 2. No effects were observed for FMD, PWV, AIx and BP.	Curtis et al. 2022
3.	A cross-over randomized controlled intervention trial	Thirty-seven (37) participants	160 g of fresh whole blueberry or 20 g of freeze-dried blueberry	One (1) week treatment followed by 1 week wash out	1. Improved plasma NO2- levels 2. No effects SBP, DBP, total cholesterol, HDL-C, LDL-C, TAG, or glucose	Wang et al. 2022
4.	Randomized cross-over design intervention	Ten (10) adult males	348 mg anthocyanins.	Ten (10) days	1. Reduced H_2O_2-induced DNA 2. No differences in endogenous DNA damage, peripheral arterial function, and nitric oxide levels.	Del Bo et al. 2013
5.	Randomized-controlled study intervention	Forty-eight (48) participants (4 males and 44 females	50 g freeze-dried blueberries (350 g fresh blueberries).	Eight (8) weeks.	1. Decrease systolic and diastolic blood pressures 2. Decreased plasma oxidized LDL 3. Decreased serum malondialdehyde and hydroxynonenal concentration 4. No effect on serum glucose levels 5. No effect on lipid profiles.	Basu et al. 2010b
6.	Double-blind, parallel placebo controlled randomized clinical trial intervention	One hundred and fifteen (115) males	75 g and 150 g blueberries (1/2 cup and 1 cup respectively).	Six (6) months	1. 1 cup improved endothelial function, systemic arterial stiffness and attenuated cyclic guanosine monophosphate concentrations. 2. ½ cup had no effect on these biomarkers.	Curtis et al. 2019
7.	Randomized, Double-Blind, Placebo-Controlled Clinical Trial.	Forty-four (44) adults	45 g of blueberry	Six (6) weeks	1. No difference in blood pressure and insulin sensitivity 2. Improved endothelial function.	Stull et al. 2015

Table 2 (continued)

S/N	Interventions	Subjects/size	Dose	Study duration	Main findings	References
8.	Randomized cross-over design interventions.	Fourteen (14) participants	75 g and 35 g	Three (3) weeks.	1. Decreased serum markers of oxidation 2. Improved antioxidant protection.	Blacker et al. 2013
9.	Randomized, double-blind, placebo-controlled clinical trial interventions.	Forty-eight (48) postmenopausal women with pre- and stage 1-hypertension	22 g freeze-dried blueberry powder	Eight (8) weeks.	1. Lowered systolic blood pressure and diastolic blood pressure and brachial-ankle PWV. 2. Improved nitric oxide levels.	Johnson et al. 2015
10.	Randomized cross-over design intervention.	Eighteen (18) male volunteers	25 g freeze-dried powder (375 mg of ACNs).	Six (6) weeks, spaced by a 6-week wash-out period.	1. Reduced levels of endogenously oxidized DNA bases and H_2O_2-induced DNA damage 2. No effect on markers of endothelial function.	Riso et al. 2013
11.	Double-blind, parallel-arm, randomized controlled trial intervention.	Fifty-two (52) men (US veterans)	22 g freeze-dried blueberries	Eight (8) weeks.	1. Lowered mean hemoglobin A1c, fructosamine, triglycerides, aspartate transaminase, and alanine transaminase 2. No effects on fasting plasma glucose, serum insulin, total cholesterol, LDL-cholesterol, HDL-cholesterol, and C-reactive protein levels, blood pressure, and body weight.	Stote et al. 2020
12.	A randomized controlled study intervention.	Twenty-five (25) subjects	250/375 g blueberry	Six (6) weeks	1. Decreased F2-isoprostanes and 5-OHMU 2. Increased plasma IL-10 and NK cell counts 3. Other markers were unaffected.	McAnulty et al. 2011
13.	Randomized, parallel-arm, double-blind, placebo-controlled clinical trial intervention.	Forty (40) pre- and stage 1-hypertensive postmenopausal women	22 g freeze-dried highbush blueberry powder per day.	Eight (8) weeks.	1. Reduced levels 8-hydroxy-2-deoxyguanosine (8-OHdG 2. Other biomarkers were unaffected	Johnson et al. 2017
14.	Randomized, controlled crossover trial intervention.	Ten (10) healthy volunteers	34 g, freeze-dried powder equivalent to 240 g of fresh blueberry.	One (1) day intervention separated by 1-week washout.	1. No differences in FMD 2. Differences in the levels of individual plasma metabolites.	Rodriguez-Mateos et al. 2014, b
15.	Randomized, controlled, double-blind, crossover human intervention trials.	Twenty-one (21) healthy men	0, 766, 1278 and 1791 mg total blueberry polyphenol	One (1) day intervention with hourly measurements for 6 hours.	1. Increased FMD 2. Decreased neutrophil NADPH oxidase.	Rodriguez-Mateos et al. 2013

Table 2 (continued)

S/N	Interventions	Subjects/size	Dose	Study duration	Main findings	References
16.	Randomized placebo-controlled crossover trial intervention	Twenty-three (23) volunteers	24.1 g and 48.2 g respectively blueberry powder.	Three (3) days and 2-weeks washout period.	1. No effects on plasma FFA and cytokine levels 2. Suppressed cytokines (IL-β, IL-6) production.	Ono-Moore et al. 2016
17.	Randomized controlled trial intervention.	Twenty-four (24) overweight and obese children	375 g/week, blueberry purée.	Eight (8) study duration.	1. Increased antioxidant levels 2. Reduced chronic markers of inflammation.	Giongo et al. 2011
18.	Randomized placebo-controlled study intervention.	Twenty-five men and post-menopausal women	250 g blueberries.	Six (6) weeks duration.	1. No effects on body mass, composition, and overall blood pressures 2. Decreased AIx and ASPs. 3. No effect on plasma redox 4. Increased absolute NK cells.	McAnulty et al. 2011
19.	Single-blind, randomized, placebo-controlled, crossover design trial intervention.	Nineteen (19) adult women at risk for type 2 diabetes	240 mL of wild blueberry juice containing 314 mg total anthocyanin.	Seven (7) days study.	1. No effects on some cardio-metabolic and inflammatory markers 2. Lowered systolic blood pressure. 3. Increased serum concentrations of nitrates and nitrites.	Stote et al. 2017

2013; Stull et al. 2015; Zhu et al. 2011). However, in some other studies, endothelial function was unaffected by blueberry consumption, possibly due to different doses of the anthocyanin-rich berries that was consumed, methods used to process the berries and methods used to assess endothelial function (Stull et al. 2015). Also, using whole blueberry powder rather than the purified anthocyanin fraction may have better benefits on endothelial functions due to synergistic interactions between different polyphenols (Stull et al. 2015).

Although, in vitro, ex vivo and animal studies support the beneficial effects of berry and their anthocyanins in modulating endothelial functions, results from human studies are inconclusive (Del Bo et al. 2013). In this study, blueberry containing 348 mg anthocyanins or a control jelly was administered to 10 study participants for a period of 10 days. It was believed that if the effects were actually mediated by blueberry anthocyanins, then the likely cause for this observation may be due to the rapid absorption and elimination of anthocyanins, typically within 3–4 h after consumption (Del Bo et al. 2013). In a subsequent long-term study in which blood samples were obtained 12 h after blueberry drink intake, no anthocyanins were detected in samples at all, confirming the earlier notion of rapid absorption and elimination of anthocyanins (Del Bo et al. 2013; Riso et al. 2013). Administering of 1 cup (150 g) of blueberries/day in to 115 adult participants with metabolic syndromes a 6 months' study resulted in sustained and clinically relevant improvements in endothelial function compared to placebo (Curtis et al. 2019). This also resulted in improved conduit artery endothelial function, measured by percent flow mediated dilatation (%FMD) with effect size of 1.06% compared with placebo by a magnitude that was reported to translate to a 13% reduction in future CVD events (Curtis et al. 2019).

Similar improvements in FMD were observed after consumption of blueberry containing buns (30 g freeze dried blueberry) or blueberry drinks (240 g fresh blueberry) in a 1-day study followed by 1-week wash out period with maximum FMD occurring 2 h after consumption of the bun and 1 h after consuming the drink, though the magnitude of the vascular effects was unaffected by processing (Rodriguez-Mateos, Del Pino-Garcia, et al. 2014). Although the exact mechanism is still unknown, however, polyphenols present in the blueberries are considered to be responsible since they account for the major bioactive components of the products. Plasma metabolites levels (ferulic acid and vanillic acid for the bun and benzoic acid and vanillic acid for the drink) 2 h after consumption correlated with FMD, suggesting association between vascular functions and plasma metabolites levels (Rodriguez-Mateos, Del Pino-Garcia, et al. 2014). This effect was attributed to the additive and synergistic effects of individual polyphenols and their metabolites. It was thought that the individual polyphenolic compounds may have biological activities that are additive in such a manner that changes in polyphenolic composition had no effect on net bioactivity. The synergistic nature of plasma phenolic metabolites and catabolites on FMD even is considered to play a role, it is however, not clearly defined.

Blueberry polyphenols and blood lipids reduction

Chronic diseases are known to be linked to higher levels of free fatty acids (FFAs), abnormal lipid metabolism and prolonged postprandial hyperlipidemia, resulting in increased concentrations of proinflammatory cytokines though the mechanism by which hyperlipidemia modulates inflammatory responses is still not fully understood (Ono-Moore et al. 2016; Wang et al. 2022; Wu et al. 2018). Polyphenols are recognized as potent inhibitors of LDL oxidation, a key mechanism in the development of atherosclerosis (Miraghajani et al. 2020; Pandey & Rizvi 2009; Wu et al. 2018). Reducing blood LDL levels and improving the LDL/HDL cholesterol ratios through the diet are vital for CVD risk management (Habauzit & Morand 2012). The ability of polyphenols to inhibit this process varies with different polyphenolic classes, for instance soy protein isolate (containing isoflavones) and green tea (a major source of flavanol) significantly reduced LDL cholesterol by 0.19 and 0.23 mmol/l respectively (Hooper et al. 2008). This LDL reduction ability is effected through several mechanisms, for instance, by inhibition of the critical steps in the absorption of fat, cholesterol, and other lipids in the intestine (Koo & Noh 2007).

Elevated levels of biomarkers of lipid and lipoprotein oxidation, for instance, malondialdehyde (MDA) and ox-LDL are commonly prevalent in populations with abdominal adiposity and metabolic syndrome disorders and are also associated with CVDs, especially CHD (Basu, Du, et al. 2010). The study involved 48 obese men and women (4 males and 44 females consuming 50 g freeze-dried blueberries (350 g fresh blueberries) in an 8-week randomized control trial. Blueberry supplementation resulted in significant decreases in plasma ox-LDL (28%), and combined serum MDA and 4-hydroxynonenal (HNE) levels (17%) compared to controls (9 and 9%) suggesting that the lipid lowering ability of blueberry is due to its antioxidant effects (Basu, Du, et al. 2010). Administering 1 cup (150 g) of blueberries/day in a 6 months' study resulted in sustained and clinically relevant improvements in HDL cholesterol concentrations (+0.08 mmol/L) (especially in statin nonusers) (Curtis

et al. 2019). These improvements, especially, increased cGMP levels, HDL cholesterol particle density ($+0.48n$, $\times 10^{-6}$), and apoA-I levels (0.05 g/L) were reported to be likely due to underlying improvements in vascular and lipid status (Curtis et al. 2019). Consumption of blueberry was considered beneficial to lower the risks of CHD and CVD in both men and women participants, and is therefore, considered an effective dietary approach to reduce CVD risk.

In a meta-analysis by Miraghajani et al. (2020) in which 11 studies were included in the final study analysis, it was discovered that supplementation of diets with blueberry had small insignificant reduction in total triglycerides (TG). The subgroup analysis however, had beneficial effects on weight, especially from longer studies that had a follow up of more than 6 weeks, or with blueberry powder or freeze-dried blueberry used. The study concluded that current evidence is insufficient to suggest beneficial roles of blueberry supplements in its ability to modify CVD risk factors across different adult populations. It however, advocated for more robust data and larger studies to enable definitive statements on the potential effects of blueberry supplements as well as applying personalized nutrition approaches to understand the roles race and ethnicity play in modulating these effects (Miraghajani et al. 2020).

Reduction in platelet activation by polyphenols

Increasing epidemiological evidence supports the notion that polyphenols-rich foods reduce the risk of arterial thrombosis (Hollman et al. 2011). Platelet activation occurs upon endothelium damage resulting in the formation of thrombus within the damaged arteries (Shaughnessy et al. 2009). This process can also be important mediators of inflammation and consequent atherogenesis. Although it is difficult to draw conclusions on this outcome due to the heterogeneity between studies as had been stated previously, chronic consumption of polyphenols from a combination of berries, especially blueberries as well as whole berries or their juices have had inhibitory effects on platelet aggregation (Erlund et al. 2008; Olas 2017; Ostertag et al. 2010; Rodriguez-Mateos, Heiss, et al. 2014). Very limited clinical studies have been conducted on platelet activation with berries so far (Curtis et al. 2009; Erlund et al. 2008; Rodriguez-Mateos, Heiss, et al. 2014). One of the studies reported no changes in menopausal women (Curtis et al. 2009) while the second study reported decreased platelet aggregation after consumption of mixed berries containing 837 mg of total polyphenols (515 mg of anthocyanins) (Erlund et al. 2008). Other studies reported the effects of berry anthocyanins on platelet but not on whole berries or more specifically, on blueberries (Thompson et al. 2017; Tian et al. 2021). More studies, especially with whole blueberries will therefore, need to be conducted to convincingly establish the ability of blueberry and its polyphenols and anthocyanins to modulate platelet activation and aggregation that could prevent cardiovascular risks and complications.

Oxidative stress reducing ability of blueberry polyphenols

Oxidative stress and the generation of free radical species is central to the pathogenesis of several CVD complications (Del Bo et al. 2022; Johnson et al. 2017; Kalt et al. 2020). Oxidative stress is caused by an imbalance between the oxidants (usually termed reactive oxygen/nitrogen species, ROS) and antioxidant (for instance, catalase, superoxide dismutase and glutathione peroxidase) in favor of the oxidants, or more specifically, when the excessive generation of ROS overwhelms the cellular antioxidant defense systems (Elks et al. 2011; Hollman et al. 2011; Maya-Cano et al. 2021; Shaughnessy et al. 2009). Excessive generation of ROS is known to cause lipid impairment, protein and DNA damage and cell-function defects (Del Bo et al. 2013; Giongo et al. 2011; Johnson et al. 2017). There is a positive correlation between the consumption of berries, especially blueberries and reduced risk for CVDs (Basu, Du, et al. 2010; Blacker et al. 2013; Del Bo et al. 2022; Habauzit & Morand 2012). Vitamins and carotenoids were initially thought to be responsible for this observed effect due to their antioxidant properties, but more recent works have focused increasing attention on polyphenols though results are inconclusive due to their structural diversity, wide distribution in foods and limitations of experimental studies (Blacker et al. 2013; Del Bo et al. 2022; Del Rio et al. 2013; Habauzit & Morand 2012). The antioxidant properties of blueberry not only reduce oxidative stress but was also reported to be one of the key mechanistic pathways responsible for the BP lowering, lipid lowering and reduction of inflammatory cytokines in adult populations with abdominal adiposity and metabolic syndromes that are at risk of CVDs (Basu, Du, et al. 2010; Johnson et al. 2017; Liu et al. 2015; McAnulty et al. 2011).

Blacker et al. (2013) reported that blueberries protected against serum oxidation independent of sugar or ascorbic acid contents when administered to 14 participants consuming a high carbohydrate, low fat diet during a 3-week cross-over study. In this study to measure postprandial markers of serum oxidation, the participants were given three treatments of high dose blueberry (75 g), low dose blueberry (35 g) and a control (ascorbic acid and sugar with dosage similar to high blueberry). The study reportedly demonstrated that a half-cup serving of blueberries adequately inhibited postprandial oxidation through

the action of its content of phenolic compounds, which is associated with direct increase in postprandial serum antioxidant capacity (Blacker et al. 2013; Snyder et al. 2011). Although the study replicated findings from previous studies, for instance, Mazza et al. (2002), Kay and Holub (2002) and Prior et al. (2007), the present study used lower doses, suggesting that a smaller dose that is more likely to be eaten by the consumers can provide equal benefits with significant increase in serum antioxidant capacity (Blacker et al. 2013).

Johnson et al. (2017) reported that daily consumption of blueberry for 4 weeks by postmenopausal women lowered BP, improved arterial stiffness, and also provided modest protection against oxidative damage although these improvements were not sustained at 8 weeks. The study evaluated effects of consuming either of 22 g freeze dried highbush blueberry powder or 22 g placebo powder per day as control by 40 postmenopausal women with pre- and stage 1-hypertension. In particular, a treatment effect was observed in DNA purified from plasma samples after 4 weeks blueberry consumption for 8-hydroxy-2′-deoxyguanosine (8-OHdG), a known biomarker of oxidative DNA damage. They concluded that the likely reason for these observed differences in activity between week 4 and week 8 may be due to acclimation to chronic blueberry consumption in their ability to reduce oxidative stress (Johnson et al. 2017). The mechanism for the protection against oxidative DNA damage was reported to be due to possibly several mechanisms, including the activation of endogenous antioxidant signaling pathways by the bioactive compounds and/or their metabolites, leading to increased expression of antioxidant gene and proteins or they acted as antioxidants themselves (Johnson et al. 2017). In view of the uncertainties surrounding the exact mechanisms responsible for these observed effects, the study recommended the use of metabolomics analyses to provide insights into the bioactive compounds in blueberries that may be responsible for these effects.

Modulation of inflammation by blueberry polyphenols

In addition to oxidative stress and the generation of free radicals and ROS, inflammation also plays a critical role in the pathogenesis of several chronic diseases, such as obesity, diabetes, neurodegeneration, certain types of cancers, and in particular, in the onset and progression of CVDs (Blacker et al. 2013; Del Bo et al. 2013; Del Bo et al. 2022; Giongo et al. 2011; Johnson et al. 2017). According to Miller et al. (2019), inflammation develops as the body's common, protective, and temporary innate immune system's response to pathogens and injury, which involve production of pro and anti-inflammatory cytokines. Examples of inflammatory cytokines include interleukins (IL-1β, IL-6), tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), fibrinogens, serum amyloid A, chemokines (monocyte chemoattractant protein, MCP-1) and adhesion molecules like the vascular cell adhesion molecules (VCAM-1) and inter-cellular adhesion molecules (ICAM) (Johnson et al. 2017; Miller et al. 2019; Ono-Moore et al. 2016). Many inflammatory biomarkers have been identified to be associated with the onset and pathogenesis of CVDs (Del Bo et al. 2022; Giongo et al. 2011; Johnson et al. 2017; Miraghajani et al. 2020). Several mechanisms have also been used to explain this pathogenesis, possibly arising from the adipose tissue, which is known to be involved in the regulatory process through the production of cytokines (Giongo et al. 2011). It may also involve increased serum triglycerides, total cholesterol, and LDL-cholesterol (Giongo et al. 2011). Therefore, controlling oxidative stress and inflammation may considerably address the attendant health complications that may be due to these detrimental biological processes (Johnson et al. 2017; Ono-Moore et al. 2016).

Bioactive compounds and polyphenols present in blueberries are reported to have several beneficial effects on human health, especially in effectively reducing the upregulation of inflammatory genes and oxidative stress in hamsters, due to their cytoprotective and anti-inflammatory properties (Basu, Du, et al. 2010; Giongo et al. 2011; Kim et al. 2010; Liu et al. 2015). Also, in a clinical study involving 24 overweight and obese children fed fresh blueberry, blueberry puree and a control without blueberry, it was demonstrated that increased consumption of blueberries resulted in higher antioxidant levels, which also correlated negatively with serum markers of inflammation (CRP, ceruloplasmin, and complements C3 and C4) and oxidative stress in overweight and obese children (Giongo et al. 2011). The study involved 24 overweight and obese children administered fresh blueberries (375 g/week), blueberry purée (375 g/week), and a control group that did not consume any blueberries in an 8 weeks study. Complementary factor C3 is reported to be a known precursor of a potent activator and chemotaxin of macrophages that is expressed in the adipocytes and involved in inflammation. Both complementary factor 3 and complementary factors 4 are major plasma proteins of the complement pathway of the immune system that are produced in response to inflammation and disease (Giongo et al. 2011). Ceruloplasmin is another inflammation biomarker protein that acts both as an antioxidant in serum by oxidizing ferrous ion and also as a pro-oxidant under low pH in tissue compartments by donating free copper, resulting in free radical generation and oxidative damage to tissues or through LDL oxidation (Giongo et al. 2011). In this study, ceruloplasmin was reported to correlate positively with CRP

with both biomarkers predictive of cardiovascular events in adults, suggesting that intervention diets with blueberry have the potential to reduce oxidative stress and inflammation and therefore, death (Giongo et al. 2011). It is important to note that while this study and several others reported on the beneficial effects of blueberry consumption on markers of inflammation, other studies (Riso et al. 2013;Stote et al. 2017 ; Stote et al. 2020) did not observe any significant effects of blueberry consumption on markers of inflammation beyond their antioxidant effect. This could possibly be due to different blueberry doses and types of blueberry powders administered to study participants, and consequently different bioactive compounds (Miller et al. 2019).

Basu et al. (2010, b) reported that the biomarkers of inflammation (CRP, IL-6, ICAM-1 and VCAM-1) were significantly elevated in metabolic syndrome and could therefore, be positively correlated with CVD while adiponectin was significantly decreased under same conditions and inversely associated with CVD. Whereas the study did not find any significant differences in anti-inflammatory cytokines with blueberry supplementation, it was however, reported that this null effect may be due to the shorter duration of the study and therefore, recommended further investigation. Similarly, daily consumption of 250 g of blueberry for 6 weeks has been associated with reduction of inflammatory cytokines in 25 adults with arterial stiffness while at the same time improving plasma anti-inflammatory cytokines levels, suggesting benefits of flavonoids consumption (McAnulty et al. 2011).

Improvements in arterial stiffness by blueberry polyphenols

It has long been known that synergy exists between endothelial dysfunction and arterial stiffness and between augmentation index (AIx) and hypercholesterolemia (Curtis et al. 2019; Del Bo et al. 2022). Administering 1 cup (150 g) of blueberries/day in a 6-month study resulted in sustained and clinically relevant improvements in systemic arterial stiffness (Curtis et al. 2019). Although aortic distensibility (pulse wave velocity, PWV) is closely associated with peripheral blood pressure, the study did not find any significant change in carotid femoral PWV (cfPWV). PWV is a non-invasive approach used to measure arterial stiffness and also to predict future cardiovascular events (Johnson et al. 2015).

Several studies have shown that foods rich in polyphenols and flavonoids improve PWV and consequently, arterial stiffness (Del Bo et al. 2022; Dohadwala et al. 2011; Johnson et al. 2015; Siasos et al. 2014). Improvements in arterial stiffness, potentially through enhanced NO mediated vasodilation were reported in a study involving 48 postmenopausal women given either 22 g freeze dried blueberry powder or 22 g control powder for 8 weeks with pre- and stage 1-hypertension, suggesting that regular consumption of blueberry has beneficial effects (Johnson et al. 2015). The dietary intervention with blueberry supplementation led to reduced brachial-ankle PWV (baPWV), which is considered a measure of central (aortic) and peripheral artery stiffness and strongly associated with the gold standard cfPWV. However, it did not reduce the cfPWV, suggesting that the dietary interventions are more effective on the peripheral arteries than the central arteries (Johnson et al. 2015; Johnson et al. 2017). Reductions in arterial stiffness were mainly attributed to improvements in the structural properties of the arterial wall requiring longer treatment period for these improvements to be noticeable compared to many biochemical markers (Johnson et al. 2017).

McAnulty et al. (2014) reported that consuming 38 g of dehydrated blueberry powder (250 g of rehydrated berries) daily for 6 weeks by sedentary adults led to significant reductions in AIx and aortic systolic pressure (ASP) that were likely attributed to contents of anthocyanin and other polyphenolic compounds. The possible mechanisms for this observed effect were reported to be due to the favorable changes in endothelial NO synthase expression and other endothelial pathway vasodilators caused by chronic blueberry supplementation, which may also likely cause more distensibility of the arterial conduit (McAnulty et al. 2014). As a consequence, the increased elasticity mitigates longer pulse wave transit time, and decreased the magnitude of the returned aortic pulse wave, suggesting that bioactive anthocyanins in blueberry mostly effected these changes through modulation of cellular signaling pathways (McAnulty et al. 2014).

Future directions

Most of the studies reviewed here have several limitations that could have negatively affected the reported outcomes or make it difficult to draw definitive conclusions. One of the reasons attributed for the lack of effect of blueberry consumption on CVD indices and biomarkers in some of the studies has been attributed to the small sample sizes and short duration (mostly less than 8 weeks) of the study designs (Blacker et al. 2013; Johnson et al. 2015; Miraghajani et al. 2020; Riso et al. 2013). While it was observed that statistical power of the study increases with number of participating subjects, they however reported that the effect of size for the study is not dependent on the sample size, suggesting the need for statistically representative sample size (Stote et al. 2017; Stote et al. 2020). In some studies, the study population was reported to be predominantly white men with metabolic syndromes, thereby making it difficult to establish if the same results can be obtained with other ethnicities and gender due to the socioeconomic and health

disparities (Curtis et al. 2019; Miraghajani et al. 2020; Stull et al. 2015). It will be interesting to conduct studies taking cognizance of these factors in order to make outcomes of such studies representative and translated to the general population. In addition, studies need to focus not only on CVD biomarkers but cardiovascular and metabolic endpoints so that definitive conclusions can be made (Basu, Du, et al. 2010; Basu, Rhone, & Lyons 2010). There are also discrepancies between the effects of consuming whole berries versus purified berry anthocyanins and possible synergistic actions with other nutrient components that need to be resolved for a proper understanding of potential mechanisms of actions (Basu, Du, et al. 2010; Basu, Rhone, & Lyons 2010; Johnson et al. 2015; Miraghajani et al. 2020). Bioavailability of freeze-dried blueberry was not measured in most of the studies as well, thereby making it difficult to ascertain the level of absorption and metabolism of the blueberry polyphenols, which may consequently affect the bioavailability and therefore, the effectiveness of these ingested blueberry polyphenolic compounds in the body (Stote et al. 2017; Stote et al. 2020). Analysis of the effects of the gut microbiota on digestion, absorption, bioavailability and metabolism of blueberry polyphenols and anthocyanins will provide definitive answers to some of these unresolved mechanisms. In many of the studies, determinations for serum biomarkers of vascular functions and plasma/urinary blueberry polyphenol metabolites were not determined, making it difficult to determine the mechanisms responsible for the improvements in cardiac and endothelial functions beyond inferences (Stull et al. 2015). A comprehensive metabolites profile involving metabolomics analyses will help us to understand the bioactive compounds in blueberries responsible for the observed effects as well as potential metabolites that can be considered biomarkers for these CVD controls and their associated potential mechanistic pathways (Johnson et al. 2017).

Conclusion

This review provides evidence from several studies supporting the CVD protective effect of blueberries. The evidence also supports the notion that this CVD protective effect of blueberry is attributed to its content of bioactive polyphenols, especially the anthocyanins. The CVD protective effects of blueberry polyphenols and anthocyanins are due to multiple mechanisms including reduction in systolic and mean arterial BP, improvement in lipid metabolism, prevention of cholesterol-induced atherosclerosis, and improvements in endothelial functions. Other mechanisms responsible for this effect are reduction of oxidative and inflammatory damage to the endothelium by suppressing oxidative stress and release of inflammatory mediators, protection against ischemic damage of the heart including cardiomyocyte survival, reduction in renal nitrite content and arterial stiffness, and reduction in platelet activation. Therefore, incorporating blueberry as a regular component of the diet may protect against CVDs, promote good nutrition and health, and prolong human life by decreasing morbidity and mortality arising from CVDs and other associated complications. Based on the studies discussed, an effective daily dose of approximately 20–30 g freeze-dried blueberry powder or 300–350 g fresh blueberries (approximately 350 mg anthocyanins) is recommended for optimum effects.

Abbreviations

CVD	Cardiovascular diseases
TAC	Total antioxidant capacity
CHD	Coronary heart disease
HBP	Hypertension or high blood pressure
CHF	Congestive heart failure
PAD	Peripheral artery disease
CHF	Congenital heart failure
LDL	Low-density lipoprotein
HDL	High density lipoprotein
TG	Triglycerides
NO	Nitric oxide
FMD	Flow-mediated dilatation
BP	Blood pressure
RHI	Reactive hyperemia index
FFA	Free fatty acids
MDA	Malondialdehyde
ROS/RNS	Reactive oxygen/nitrogen species
8-OHdG	8-hydroxy-2′-deoxyguanosine
TNF-α	Tumor necrosis factor-alpha
CRP	C-reactive protein
MCP-1	Monocyte chemoattractant protein
VCAM-1	Adhesion molecules like the vascular cell adhesion molecules
ICAM	Inter-cellular adhesion molecules
AIx	Augmentation index
PWV	Pulse wave velocity
cfPWV	Carotid femoral PWV
baPWV	Brachial-ankle PWV
ASP	Aortic systolic pressure

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Authors' contributions

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Availability of data and materials

All data generated during this study are included in this published article. Further details are available from the corresponding author upon reasonable request.

Declarations

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Not applicable.

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