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Invited Review Article

Antioxidant properties of anthocyanins and their mechanism of action in atherosclerosis☆

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ABSTRACT

Atherosclerosis develops due to lipid accumulation in the arterial wall and sclerosis as result of increased hyperlipidemia, oxidative stress, lipid oxidation, and protein oxidation. However, improving antioxidant status through diet may prevent the progression of atherosclerotic cardiovascular disease. It is believed that polyphenol-rich plants contribute to the inverse relationship between fruit and vegetable intake and chronic disease. Anthocyanins are flavonoid polyphenols with antioxidant properties that have been associated with reduced risk of cardiovascular disease. The consumption of anthocyanins increases total antioxidant capacity, antioxidant defense enzymes, and HDL antioxidant properties by several measures in preclinical and clinical populations. Anthocyanins appear to impart antioxidant actions via direct antioxidant properties, as well as indirectly via inducing intracellular Nrf2 activation and antioxidant gene expression. These actions counter oxidative stress and inflammatory signaling in cells present in atherosclerotic plaques, including macrophages and endothelial cells. Overall, anthocyanins may protect against atherosclerosis and cardiovascular disease through their effects on cellular antioxidant status, oxidative stress, and inflammation; however, their underlying mechanisms of action appear to be complex and require further elucidation.

1. Introduction

1.1. Atherosclerotic cardiovascular disease

Atherosclerosis is an inflammatory disease that results in the accumulation of lipid and the hardening of arteries, usually stemming from hyperlipidemia and lipid oxidation, and is a major cause of mortality [1]. Atherosclerotic cardiovascular disease (CVD) includes two major cardiovascular events: ischemic heart disease and stroke, the world's first and third leading causes of death, comprising 85% of cardiovascular deaths and 28% of all-cause mortality [2]. Lipoprotein metabolism, oxidative stress, and inflammation play an interactive role in the development of CVD and thus, are key targets of both diet and pharmacotherapies aimed at CVD prevention and treatment. There is a clear link between CVD and low-density lipoprotein (LDL) abundance in serum [3]. Any mechanism lowering LDL particle concentrations in circulation should reduce the risk of CVD proportional to the reduction in LDL-cholesterol (LDL-C) and cumulative duration of exposure to LDL-C [3]. Increased LDL-C progressively harms the arterial wall [4], as lipids can become trapped, resulting in oxidation, aggregation, and eventual deposition of cholesterol crystals in the intima and underlying smooth muscle of the artery. LDL retention increases its concentration and exposure to arterial walls which promotes its oxidation [1], resulting in increased concentrations of oxidized LDL (oxLDL) which heighten the risk of CVD [3]. The presence of oxidized lipoproteins in the arterial wall stimulates an inflammatory response in which monocytes will adhere to endothelial cells expressing adhesion molecules and selectins for monocyte recruitment [1]. Once in the intima, monocytes differentiate into macrophages that take up accumulated lipids and oxLDL initiating the formation of foam cells. Other immune cells can also become activated by cytokines and accumulate alongside foam cells within the plaque, where they exacerbate inflammatory signaling and facilitate atherosclerosis development [5,6]. Foam cells can undergo apoptosis and when coupled with impaired efferocytosis, it can promote the development of a lipid-rich necrotic core in the atherosclerotic lesion. Chronic inflammation can also result in the oxidation of high-density lipoproteins (HDL), hindering its ability to perform reverse cholesterol transport (RCT) as well as protect lipoproteins and the endothelium from oxidation [7,8]. As a consequence, atheromatous plaques grow and influence the surrounding fibrous tissues and smooth muscle, hindering arterial blood flow. The addition of connective tissue

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Abbreviations

CVD	Cardiovascular disease
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
oxLDL	Oxidized LDL
HDL	High-density lipoprotein
RCT	Reverse cholesterol transport
HDL-C	High-density lipoprotein cholesterol
CHD	Coronary heart disease
TAC	Total antioxidant capacity
PCA	Protocatechuic acid
PGA	Phloroglucinaldehyde
ROS	Reactive oxygen species
Trolox	6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic
TEAC	Trolox equivalent antioxidant capacity
ORAC	Oxygen radical absorbance capacity
DPPH	2,2-diphenyl-1-picryl-hydrazyl-hydrate
ABTS	2,2-azino-bis(3-etilbenzotiazolin)-6-sulfonic acid radical cation
FRAP	Ferric reducing ability of plasma
CUPRAC	Cupric reducing antioxidant capacity
FCR	Folin-Ciocalteu reducing capacity
HAT	Hydrogen atom transfer
SET	Single-electron transfer
TAS	Total antioxidant capacity
HFD	High fat diet
ACW	Anti-radical capacity of water-soluble substances
ACL	Anti-radical capacity of lipid-soluble substances
SOD	Superoxide dismutase
CAT	Catalase
GPx	Glutathione peroxidase
Trx	Thioredoxin antioxidant system
$ApoE^{-/-}$	Apolipoprotein E knockout
VCAM1	Vascular cell adhesion molecule 1
MCP-1	Monocyte chemoattractant protein 1
TrxR	Thioredoxin reductase
NO	Nitric oxide
GSH	Glutathione
HOCl	Hypochlorous acid
Nrf2	NF- E_2-related factor 2
ARE	Antioxidant response element
GR	Glutathione reductase
GST	Glutathione-S-transferase
HO-1	Heme oxygenase 1
NQO1	NAD(P)H quinone reductase
ERK1/2	Extracellular signal-regulated kinase 1/2
JNK	c-Jun-N-terminal-kinase
SD	Sprague Dawley
HMDM	Human monocyte-derived macrophages
SOD1	Cu/Zn-SOD1
SOD2	Mn-SOD
MetS	Metabolic Syndrome
eNOS	Endothelial nitric oxide synthase
MPO	Myeloperoxidase
XO	Xanthine oxidase
NOX	NADPH oxidase
iNOS	Inducible nitric oxide synthase
BAE	Blueberry anthocyanin extract
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
TNFα	Tumor nuclear factor alpha
IKK	IκB kinase
COX2	Cyclooxygenase 2
PBMC	Peripheral blood mononuclear cells
RNS	Reactive nitrogen species
PL	Phospholipid
apoB100	Apolipoprotein B100
MDA	Malondialdehyde
TBA	Thiobarbituric acid
TBARS	TBA reactive substances
Cu	Copper
PPAR	Peroxisome proliferator-activator receptor
iso-PGF2α	Iso-prostaglandin 2-alpha
AOPPs	Antioxidant oxidation protein products
MAPK	Mitogen-activated protein kinase
4-HNE	Aldehyde 4-hydroxynonenal
CD36	Cluster of differentiation 36
LOX1	Lectin-type oxLDL receptor
CRP	C-reactive protein
PON2	Paraoxonase 2
AP-1	Activator protein-1
TLR4	Toll-like receptor 4
HAECs	Human aortic endothelial cells
BH_4	Tetrahydrobiopterin
ER	Endoplasmic reticulum
HUVEC	Human umbilical vascular endothelial cells
GSSG	Oxidized glutathione
ABCG1	ATP-binding cassette transports sub-family G member 1
LXRα	Liver X receptor alpha
ABCA1	ATP-binding cassette transports sub-family A member 1
RCT	Reverse cholesterol transport
SR-B1	Scavenger receptor class B type 1
apoA-I	Apolipoprotein A-I
LCAT	Lecithin-cholesterol acyltransferase
VLDL	Very low-density lipoprotein
LPL	Lipoprotein lipase
CEC	Cholesterol efflux capacity

produced by fibroblasts as well as the deposition of calcium in the lesions leads to sclerosis, or hardening of the arteries [1]. Excessive macrophage and endothelial oxidative stress exacerbates this process, however, improvements in HDL function can help to prevent CVD. Therefore, it is imperative to identify dietary components that improve these parameters to mitigate CVD risk.

1.2. Anthocyanins and their metabolites as atheroprotective components of the diet

Anthocyanins are of particular interest as dietary compounds due to their potential bioactivities in affecting redox status, although their daily intake among U.S. adults is relatively low (~3 mg/day) [9]. Anthocyanins are flavonoid polyphenols naturally occurring in plants and are partially responsible for the pigmentation of berries [10,11]. The major anthocyanins found in the human diet are glycoside forms of anthocyanidins, which include pelargonidin, cyanidin, delphinidin, peonidin, petunidin, and malvidin [11]. There is an inverse correlation between fruit and vegetable intake and CVD believed to be, in part, due to their polyphenol content, such as anthocyanins [12]. Anthocyanins were once thought to be poorly bioavailable; however parent compounds are immediately absorbed and transformed into bioactive metabolites that stay in circulation [13,14]. Thus, the bioavailability of anthocyanins is higher than previously thought when considering their biotransformation. Consumption of dietary anthocyanins has been associated with reduced CVD risk factors, alongside a lower risk of

coronary heart disease (CHD) and CVD mortalities [15–17]. While the effects of anthocyanins on serum cholesterol is not the focus of this review, it is still noteworthy to report their influence, since HDL-cholesterol (HDL-C) and LDL-C are independent risk factors for CVD and could interact with redox pathways in this disease process [18,19]. Evidence from a cross-sectional population-based study (n = 4039) demonstrated that U.S. adults with higher dietary total antioxidant capacity (TAC) had improved serum lipid profiles [20]. In regards to pre-clinical studies, rabbits and rats have experienced increases in HDL-C when placed on inflammatory diets in combination with anthocyanins (high cholesterol [21], high fat/high cholesterol [22], or high sucrose [23]). Thus, the state of inflammation may be important to see an effect with anthocyanins. Clinical studies have demonstrated similar changes in HDL-C with anthocyanins, typically, with increases observed after 12–24 weeks of supplementation in dyslipidemic [24], hypercholesterolemic [25], or diabetic [26] adults, which was corroborated by a meta-analysis which included additional studies than those already mentioned [27]. Anthocyanin supplementation has had similar hypolipidemic effects on LDL-C in pre-clinical and clinical models, confirmed by a meta-analysis and systematic reviews of several randomized controlled trials [26,28–31].

As previously mentioned, anthocyanins are transformed into bioactive metabolites quickly upon absorption. A small percentage of anthocyanins may be absorbed through the gastric wall indicative by the presence of the parent anthocyanin form in plasma shortly after ingestion [32]. In the small intestine, anthocyanin glycosides are readily absorbed but also may be effluxed back into the lumen by various transporters [33,34]. Unabsorbed anthocyanins that pass through to the colon can either undergo degradation or hydrolysis by colonic microbiota into metabolites and phenolic acids [35,36]. Anthocyanins have been found in several metabolized forms in plasma, urine, and bile, such as glucuronidated, sulfated, or methylated forms, indicating extensive biotransformation and distribution throughout the body [36–38]. In addition, the most common metabolite of cyanidin-3-glucoside, protocatechuic acid (PCA), has been identified in fecal samples indicating that anthocyanins may interact with the gut microbiota [39]. Maximal concentration of phenolic metabolites can range from 10 to 2000 nM at 2–30 h after consumption [40]. Anthocyanins can be metabolized to phloroglucinaldehyde (PGA) and PCA, although PCA metabolites make up a larger portion compared to PGA [41]. PCA appears to retain the antioxidant and anti-inflammatory properties of its parent form that may contribute to its anti-atherogenic properties [42]. Other anthocyanins, such as malvidin-3-glucoside can be metabolized to phenolic compounds, two major ones being hippuric and ferulic acid [40]. In healthy men, a 721 mg oral dose of cyanidin-3-glycoside appeared as over two thirds conjugated metabolites in both serum and urine compared to the parent form [14]. Total serum anthocyanin concentration hit a maximum of 96.08 nmol/L after 2.8 h [14]. Thus, it is clear that anthocyanins are metabolized and transformed into bioactive metabolites that may also exert a protective effect. Much of the research surrounding anthocyanins and their metabolites has focused on their hypolipidemic effects; however, the following review will specifically focus on their effects on measures of the antioxidant defense enzyme system, lipoprotein redox status, as well as lipid peroxidation and oxidative stress in cell, animal, and human models relevant to CVD progression.

2. Antioxidant effects and regulation of redox state by anthocyanins

2.1. Total antioxidant capacity

Anthocyanins may directly or indirectly affect redox status and, therefore, it is important to determine whether dietary anthocyanins impact the antioxidant capacity of serum. TAC, in this context, is the ability of all antioxidants found in plasma to scavenge free radicals [43]. Plasma components, such as anthocyanins, can neutralize reactive oxygen species (ROS) directly through the donation of a hydrogen or electron. The minimization of the interaction between ROS species and other compounds like metal ions or lipids can prevent further oxidation and the formation of harmful compounds [43]. Plasma antioxidant status can be altered by either ROS levels or plasma antioxidant levels, with the latter being linked to dietary TAC [43–45], which has been shown to enhance plasma TAC [46]. In addition, an inverse relationship has been found between dietary TAC and all-cause mortality and CVD mortality [47,48]. There are ways to directly measure TAC, such as through evaluating 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox) equivalent antioxidant capacity (TEAC) and oxygen radical absorbance capacity (ORAC) or by the 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) assay and TAC assay using 2,2-azino-bis(3-etilbenzotiazolin)-6-sulfonic acid radical cation (ABTS) [49–51]. There are also indirect assays such as the ferric reducing ability of plasma (FRAP) and the cupric reducing antioxidant capacity (CUPRAC), which measures the ability to reduce a metal complex [52–54]. There are several other modified assays to measure plasma antioxidant status such as total radical-trapping antioxidant parameter, total antioxidant status, Folin-Ciocalteu reducing capacity (FCR), and more. When compared against the DPPH, FRAP and ORAC assay, the ABTS method was negatively correlated with urinary 8-isoprostanes and thus may be a more effective method in predicting antioxidant status [55].

Anthocyanins can display direct antioxidant activity towards ROS by two general mechanisms – hydrogen atom transfer (HAT) and single-electron transfer (SET). With regards to the HAT mechanism, the antioxidant donates a hydrogen atom (proton and electron) to the free radical, therefore converting it to a more stable product [56]. This reaction converts the antioxidant to a radical itself, but one that is much less reactive than the initial free radical and thus the oxidation process is inhibited overall. In the SET mechanism, the free radical is stabilized through the acceptance of an electron from the antioxidant, with the antioxidant molecule itself becoming a radical cation intermediate [56]. Similar to the HAT mechanism, the newly generated antioxidant radical is more stable than the initial free radical. Anthocyanins can display direct antioxidant activity related to the presence of various substituents on their three-ring structure. The hydroxyl (-OH) groups can serve as hydrogen donors in redox reactions, while methoxyl (-OCH3) groups are thought to contribute by an intramolecular electron donor effect [57]. In the presence of lipid peroxyl radicals, anthocyanins are converted to a free radical intermediate during the inhibition of the peroxidation process [57]. The efficiency of peroxyl radical trapping by various anthocyanins was related to the B ring substituents and displayed the rank order of –OH > -OCH3 ≫ –H [57]. For example, delphinidin 3-glucoside, which has two –OH substituents in position 3′ and 5′ on its B ring, was found to be eight-fold more efficient than pelargonidin 3-glucoside which had two –H substituents on its B ring [57]. Antioxidant activity methods primarily utilize HAT and SET based assays. In HAT-based assays, the antioxidant and substrate compete for peroxyl radicals [58]. In SET-based assays, an antioxidant's capacity to participate in one-electron redox reactions is measured through a color change of the reduced oxidant [58]. HAT-based assays include TRAP and ORAC, while SET-based assays include FRAP and TAC. DPPH and ABTS assays may involve both SET and HAT reactions [58].

Anthocyanin consumption in pre-clinical rat and rabbit models have resulted in increases in serum TAC, total antioxidant status (TAS), TEAC, and DPPH [31,59–64]. *Aronia melanocarpa* extract supplementation (50 mg/kg daily) for 12 weeks enhanced hepatic TEAC in C57BL/6 mice [65]. A polyphenolic extract from blackcurrant pomace (1.5%) given to high fat diet (HFD)-fed rabbits increased the anti-radical capacity of water soluble substances (ACW) and tended to increase anti-radical capacity of lipid soluble substances (ACL) in serum [62]. ACW was also increased in response to 60 mg/kg anthocyanin-rich tart cherry extract daily for 6 weeks in HFD-fed mice [66]. However, a few studies did not find an effect on anthocyanin feeding on FRAP in animals [63,

67]. The same effect, increased TAS, has been seen among clinical populations with increases in TAC, TRAP, TEAC, FRAP, ORAP, and DPPH measures [15,26,68–74]. Consumption of wild blueberries (100 g) and *Clitoria ternatea* flower (1 g and 2 g) has also been shown to enhance postprandial antioxidant status in healthy adults after 1 h and 30 min, respectively [75,76]. Few studies have reported no effects of anthocyanins on plasma and urine antioxidant status in humans [10,70,77]. Interestingly, 200 mL/day açai juice consumption (221.58 mg anthocyanins and 99.85 mg monomeric ACN) for 4 weeks in healthy adults increased TAC [68]. Lastly, anthocyanins were shown to protect against postprandial oxidation of erythrocytes in healthy adults up to 2 h after intake of an anthocyanin-rich fruit and berry juice blend (177 μg/mL anthocyanins) [78]. Based on the preceding evidence, anthocyanins improve postprandial and long-term total antioxidant status confirmed by multiple measures. Therefore, increased serum TAS may be protective against atherosclerosis as atherosclerotic patients were found to have decreased TAS [79].

2.2. Antioxidant defense enzyme system

The body has an antioxidant defense system equipped with enzymatic and non-enzymatic antioxidants. Enzymatic antioxidants include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and the thioredoxin antioxidant system (Trx) [80]. A majority of ROS are derived from superoxide, therefore SOD is critically important to catalyze the degradation of superoxide to form oxygen and hydrogen peroxide [81]. As a result, SOD has been shown to prevent peroxynitrite formation and reduces aortic F2-isoprostanes in apolipoprotein E (apoE) knockout ($^{-/-}$) mice [82,83]. CAT significantly reduces oxidative stress by further breaking down hydrogen peroxide into molecular oxygen and water [84]. Increased CAT expression has been shown to inhibit aortic smooth muscle cell proliferation [85]. In addition, CAT and SOD may reduce oxLDL and oxLDL-induced apoptosis [86]. GPx is the main hydrogen peroxide scavenging enzyme during chronic stress that catalyzes the reduction of hydrogen peroxide and hydroperoxides to water or alcohols [87]. Hydrogen peroxide increases leukocyte adhesion via vascular cell adhesion molecule (VCAM1) expression and monocyte chemoattractant protein (MCP-1); therefore, increased GPx activity inhibits their expression [88–90]. Trx is composed of NADH, thioredoxin reductase (TrxR), and Trx which catalyzes the NADPH-dependent reduction of oxidized Trx [91]. TrxR increases nitric oxide (NO) bioavailability by increasing the ability of endothelial cells to scavenge ROS, therefore decreasing oxidative stress [92]. NADPH maintains CAT in the active form and is also used by Trx as a cofactor for the formation of glutathione (GSH) [91]. The body's secondary antioxidant defense mechanism involves exogenous non-enzymatic antioxidants such as vitamin E, vitamin C, carotenoids, polyphenols, and GSH [93]. GSH is a cofactor for GPx and can scavenge hydroxyl radical, peroxynitrite, and hypochlorous acid (HOCl), which can oxidize HDL impairing its function [94,95]. The expression of several enzymes mentioned are modulated by the NF-E_2-related factor 2 (Nrf2)-antioxidant response element (ARE) pathway which is induced by ROS as a protective mechanism in macrophages, foam cells, and endothelial cells [96–98]. Activation of the Nrf2-ARE pathway promotes the transcription of several genes involved in the antioxidant defense system including glutathione reductase (GR), GPx, glutathione-S-transferases (GST), TrxR, heme oxygenase 1 (HO-1), and NAD(P)H quinone reductase (NQO1) [99]. Nrf2 can either be activated by directly targeting the Nrf2-keap1 complex or indirectly by phosphorylation of extracellular signal-regulated kinase (ERK)1/2, which promotes the nuclear translocation of Nrf2 [100,101]. Together these antioxidants work to reduce the body's oxidative state and therefore attenuate atherosclerosis.

A number of studies have reported that anthocyanins may increase the abundance and/or activity of enzymes associated with the endogenous antioxidant defense system [102–104]. *In vitro* exposure to anthocyanin-rich extracts as well as purified anthocyanins increased CAT, GPx, and SOD enzyme activities in pancreas, liver, and endothelial cells [105–108]. Although one study did not find a difference in GPx after black rice extract administration (5 mg/mL for 24 h) in HepG2 cells [107], another found that chokeberry extract (1, 5, and 10 μM cyanidin-3-*O*-galactoside) increased GSH content in pancreatic β cells exposed to hydrogen peroxide and high glucose for 24 h [105]. However, it is important to take into consideration that anthocyanin-rich extracts may contain other physiologically irrelevant components for *in vitro* studies, such as fibers. In addition, *in vitro* studies cannot account for anthocyanin bioavailability including the extensive transformation of anthocyanins to its metabolites by the gut microbiota [109]. Out of those enzymes, GPx is most noteworthy when talking about HDL function, since one of its isoforms is strongly associated with HDL in circulation [110]. The effect of anthocyanins on GPx seems to be controversial as there are several contradictory studies. In pre-clinical models, the greatest effect is seen in hepatic GPx expression in rodents and hamsters, whereas minimal changes are seen in serum GPx activities [104,111]. While some studies did not see an effect [59,107], consumption of anthocyanin-rich foods in several animal models resulted in increased hepatic GPx expression [21,60,64,103,111–116]. Increases in GPx activity in response to anthocyanins may be dependent on the c-Jun-N-terminal-kinase (JNK)-mediated Nrf2 activation, since anthocyanin metabolites behave in such a manner [117]. Consumption of anthocyanin-rich purple sweet potatoes increased hepatic Nrf2 expression in Sprague Dawley (SD) rats [118]. Increases in GPx activity were also seen in both healthy and at risk populations [68,69], while most studies did not see an effect [102,107,119,120]. The same pattern is seen in GSH concentrations, with no change after anthocyanin consumption in humans [119] but increases seen in liver in most animal studies [21,60,112,116,118], with the exception being two studies that used anthocyanin-rich red potato flakes [59,64]. However, Rosenblat et al. did report that pomegranate juice consumption (50 mL/day for 3 months) increased total serum thiols, which includes GSH, in diabetic patients [121]. Cellular GSH content increased as well in human monocytes-derived macrophages (HMDM) from the same individuals [121]. Meanwhile, it was shown that hepatic and intestinal GST activity remains unchanged after anthocyanin supplementation in apoE$^{-/-}$ mice [111], while it is increased in rat livers [118]. In adult men with CVD risk factors, a wild blueberry drink providing 375 mg of anthocyanins did not alter GST activity after consumption for 6 weeks [122]. Anthocyanins also affect CAT and SOD activity and expression differently in pre-clinical and human models. Serum CAT activity increases in response to anthocyanins in animal models [31,60,103,111,123] while humans studies have reported increased [68,69], decreased [102] or similar CAT activity to controls [119,120]. Hepatic CAT expression typically did not change after anthocyanin consumption [59,64,111–113], although increases have been reported [30,107,116,124]. On the other hand, except for two studies [67,111], anthocyanins reportedly enhance hepatic/serum SOD expression/activity in pre-clinical models [30,31,65,66,103,104,107,113,114,123,124]. More specifically, anthocyanin-rich red potato flakes increased hepatic Cu/Sn-SOD (SOD1) and Mn-SOD (SOD2) mRNA expression in male F344 rats [59,64]. SOD1 and SOD2 expression however, was not altered by black rice extract or dietary açai in C57BL/6 mice and streptozotocin-induced diabetic mice, respectively [107,112]. Lastly, reports of SOD activity in clinical trials are mixed. Increases in activity were seen in healthy adults [69,125], dyslipidemic patients [126], and patients with metabolic syndrome (MetS) [102] after anthocyanin consumption; however, in healthy females/males and former smokers, SOD activity remained unchanged [68,119,120,122]. Although there is more evidence to support anthocyanin enhancement of antioxidant defense systems in pre-clinical models, anthocyanin consumption still had a beneficial effect in some clinical populations. More research is warranted to investigate the effect of anthocyanins on antioxidant defense in different clinical populations and its underlying mechanisms.

2.3. Oxidative stress markers

Oxidative stress, apparent by the increased production of ROS and oxLDL, has a major role in the progression of CVD [127]. Oxidative stress mainly occurs when there is an increased generation of ROS alone or in combination with the body's reduced ability to defend against oxidants. In turn, oxidative stress can lead to dysmetabolism and inflammation promoting chronic disease development, such as in atherosclerosis [128]. The body has many enzymes that generate ROS under both normal and pathological conditions, such as uncoupled endothelial nitric oxide synthase (eNOS), myeloperoxidase (MPO), xanthine oxidase (XO), lipoxygenases, and perhaps most importantly, NADPH oxidase (NOX) [129]. As a consequence of NOX activation, an electron is transferred from NADPH to molecular oxygen to form a superoxide anion [130]. Deletions of NOX1 and NOX2 in mouse models have been associated with reductions in atherosclerosis, while NOX5 is found to be upregulated in human atherosclerotic lesions [131–133]. NO is produced by activated eNOS and can be protective against atherosclerosis as, for example, it can prevent the oxidation of LDL [134]. However, eNOS can become dysfunctional during states of oxidative stress and can uncouple oxygen reduction from NO synthesis producing superoxide anions [135]. Dysfunctional eNOS and diminished NO generation are characteristic of a dyslipidemic state [136,137]. Inducible NOS (iNOS) is considered proatherogenic and induced during states of inflammation and oxidative stress which can contribute to the uncoupling of eNOS [138]. Oxidative stress can lead to lipid and lipoprotein oxidation, macrophage oxidative stress, foam cell formation, and endothelial cell oxidative stress which can ultimately promote the development of atherosclerosis.

Studies which show direct antioxidant effects of anthocyanins have been typically conducted *in vitro* using various immortalized cell lines. Huang et al. treated human retinal capillary endothelial cells with 10 μg/mL blueberry anthocyanin extract (BAE), malvidin, and malvidin-3-galactoside and found that, overall, NOX4 expression was lowered while NO levels increased [106]. In addition, eNOS activity was decreased in cells treated with BAE and its constituents [106]. In hepatic, intestinal, epithelial, and peripheral mononuclear blood cells, anthocyanin administration decreased ROS production [78,106,107,139], while cells treated with anthocyanin-rich extracts saw reductions in the generation of superoxide [107,140]. Cremonini et al. treated Caco2 cells with anthocyanin metabolites and a mix of anthocyanins which prevented phosphorylation of p65, the active subunit of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), and ERK1/2 after a tumor necrosis factor alpha (TNFα) stimulus [141]. The potent effects of anthocyanins have also been reported in animal studies. Cyanidin and delphinidin, two major anthocyanidins in human diets, decreased hepatic phosphorylation of JNK, IκB kinase (IKK), and NFκB including decreased NFκB DNA binding in C57BL/6 mice fed a HFD and anthocyanin mix while no differences were seen in mice fed the control diet with anthocyanins [142]. Anthocyanin supplementation in mice fed a HFD for 14 weeks resulted in decreased hepatic NOX3 and NOX4 expression and ileal and hepatic NOX1 and NOX4 expression [141,142]. In addition, consumption of purple sweet potato in SD rats increased hepatic NQO1 expression and decreased translocation of NFκB [118]. In SD rats fed a HFD supplemented with mulberry extract (0.15% cyanidin-3-ruinoside) for 14 weeks, aortic superoxide, peroxynitrite, nitrotyrosine, and mitochondrial superoxide production were diminished, while NO levels increased [140]. Similarly, hepatic NO levels increased in a D-galactose-induced aging-murine model fed 0.5% chokeberry for 30 days [113]. Furthermore, mulberry extract increased Thr-495 and Ser-1177 phosphorylation, which is involved in the recoupling of eNOS in endothelial cells [140,143,144]. Superoxide anion accumulation may reduce NO bioavailability and promote the conversion of NO into peroxynitrite, causing endothelial dysfunction [140]. Anthocyanins have also decreased ROS levels in F344 rats supplemented with 2% açai for 30 days, as well as superoxide levels in cardiac and thoracic samples from golden Syrian hamsters fed raspberry juice (218–305 μg anthocyanins/mL) for 12 weeks [112,114]. In addition, supplementation with cyanidin-3-glucoside (2 g/kg diet) in apoE$^{-/-}$ mice for 8 weeks resulted in reduced aortic superoxide [145]. Similarly, consumption of anthocyanin-rich foods in several animal models resulted in decreased hepatic and aortic iNOS and ileal NOS2 expression and lower hepatic cyclooxygenase 2 (COX2) expression [118,141,146]. Lastly, anthocyanin rich-extract decreased hepatic HO-1 expression in SD rats [118]. In contrast, grape consumption (77 mg anthocyanins daily) in men with MetS but not dyslipidemia had increased peripheral blood mononuclear cells (PBMC) iNOS expression after 4 weeks [147]. Polymorphonuclear cells ROS levels also decreased in response to an anthocyanin-rich juice blend in healthy adults [78]. However there are several studies were there are no responses seen in ROS [70,148,149] or homocysteine [119] levels in healthy adults and those with chronic disease. It is clear that anthocyanins attenuate oxidative stress and dampen proinflammatory signaling in pre-clinical models, while the evidence in clinical models needs to be further investigated.

2.4. Lipid and protein oxidation

Oxidative modification of carbohydrates, lipids, and proteins can result after interactions with ROS and reactive nitrogen species (RNS) [150]. ROS can impair the cellular function of lipids, potentially initiated postprandially, leading to lipid peroxidation and LDL oxidation [127]. Phospholipids (PL) and cholesterol present in LDL can undergo oxidation and potentiate further oxidative damage [151]. Products of lipid peroxidation on LDL can promote oxidative modification of apolipoprotein B100 (apoB100), altering its ability to bind to the LDL receptor [152]. The most mutagenic product of lipid peroxidation is malondialdehyde (MDA), which is a common measure of oxidative stress using its reaction with thiobarbituric acid (TBA) in a thiobarbituric acid reactive substances (TBARS) test [153,154]. F_2-isoprostanes are products of the peroxidation of arachidonic acid and have been accepted as a well-known biomarker of lipid peroxidation [155]. F_2-isoprostanes have been found to be localized in foam cells in atherosclerotic lesions and are also increased in atherosclerotic lesions [156,157]. Under normal conditions, cells have the ability to adapt to the stress and trigger signaling pathways to upregulate the body's antioxidant defense system [151]. However, when lipid peroxidation rates exceed the cell's ability for repair, apoptosis occurs facilitating the development of atherosclerosis [151].

There is sufficient evidence that anthocyanins protect against lipid peroxidation in pre-clinical models and clinical models. Anthocyanin-rich black rice extract (5 mg/mL) and hibiscus-derived anthocyanin-rich extract (100 μg/mL anthocyanins) inhibited copper (Cu)-induced LDL oxidation [107,158]. As stated previously, data from studies using anthocyanin-rich extracts need to be interpreted cautiously. In addition, mulberry-derived anthocyanin extract (0.89 mg/mg) inhibited *in vitro* Cu-induced LDL oxidation, mitigated apoB fragmentation, and reduced TBARS [159]. Anthocyanins from purple sweet potato, grape and grape seed extract also attenuated *in vitro* LDL oxidation [160,161]. Decreases in serum oxLDL concentrations have also been seen in MetS populations and pre- and post-menopausal women [149,162,163], even though some studies have reported no effects in healthy adults and those at risk for CVD [71,164]. Consumption of pomegranate juice in healthy adults lowered LDL oxidation after 1 year which was further reduced after 3 years [165]. Mulberry extract in SD rats and black rice consumption in rabbits decreased oxLDL and oxLDL susceptibility, respectively [22,140]. Anthocyanins have reduced the presence of oxLDL particles in plasma, which can be attributed to an induction in hepatic peroxisome proliferator-activator receptor (PPAR)-α and PPAR [21]. Anthocyanins also combat against lipid peroxidation in preclinical and clinical models. In apoE$^{-/-}$ mice fed cyanidin-3glucoside (2 g/kg) for 8 weeks, aortic lipid peroxidation was reduced [145]. Serum and hepatic MDA levels

were significantly reduced in animals fed diets with anthocyanin-rich foods and extracts [21,30,31,103,104,115,116,118,166–168]. Song et al. fed D-galactose-induced aging-mice 0.5% chokeberry for 30 days which resulted in diminished serum and hepatic, increased renal MDA levels while brain MDA remained unaltered [113]. Interestingly, mulberry extract reduced MDA in aortas of mice fed a HFD [140]. Serum MDA is typically reduced after anthocyanin consumption in healthy and dyslipidemic individuals [69,73,75,92,169], although urine MDA is less responsive [75,119]. Several studies discovered decreases in serum and hepatic TBARS after anthocyanin consumption in pre-clinical models [22,59–62,64,107,112,118,124,160,166,170]. Purple sweet potato consumption in HFD-fed apoE$^{-/-}$ mice tended to have lower renal TBARS [160]. Although, red potato consumption in rats did not affect hepatic TBARS and anthocyanin-rich wheat did not affect serum, hepatic, or colonic TBARS in rats [59,63]. In subjects with atherosclerosis (65–75 years old), intake of pomegranate juice reduced serum lipid peroxidation after 1 year and further reduced levels after 3 years [165]. Anthocyanin intake decreased serum lipid peroxidation by TBARS in healthy individuals, and with those with diabetes and MetS [74,78,102,121], although consumption of pigmented potato did not affect serum TBARS in healthy men [171]. Postprandial fruit juice blend consumption inhibited TBARS at 2 h post-consumption in healthy adults [78]. However, the most evidence of anthocyanin's effect on iso-prostaglandin 2-alpha (iso-PGF2-α) is seen in populations at risk for cardiovascular disease, with reductions observed in serum and urine concentrations [26,73,126,163,172–174]. Agraz and anthocyanin-rich beverage consumption in healthy adults and adults with MetS, respectively, did not see effects in serum isoprostane levels [74,77]. Anthocyanin-rich chokeberry fed to apoE$^{-/-}$ mice did not affect hepatic isoprostane levels [111].

Protein oxidation also occurs in plaques including HOCl-mediated reactions in advanced plaques [175]. Advanced oxidation protein products (AOPPs) promotes oxidative stress and thus accelerates the progression of atherosclerosis [27]. *In vitro* studies show that AOPPs upregulate receptor activator NFκB ligand in a JNK/p38 mitogen-activated protein kinase (MAPK)-dependent as well as induced the phosphorylation of NFκB [176,177]. Anthocyanins may decrease AOPPS and therefore reduce ROS levels and downregulate inflammatory signaling pathways [178]. In clinical models, an anthocyanin-rich beverage decreased postprandial AOPPs in healthy adults however [179], agraz consumption did not affect AOPPs levels in adults with MetS [172]. While the only effect seen in preclinical models is decreased renal AOPPs levels in response to anthocyanin-rich wheat diet [63]. The same diet did not affect serum, hepatic, or colon AOPPs levels [63]. Protein carbonylation occurs when protein oxidation is catalyzed by ROS [180]. Dietary açai given to F344 rats and anthocyanin supplemented mice exhibited decreased hepatic carbonyl proteins [112,167]. In a clinical trial, a purified anthocyanin supplement given to diabetic subjects decreased serum protein carbonyls after 24 weeks [26]. Lastly, aldehyde 4-hydroxynonenal (4-HNE) can form protein adducts during states of oxidative stress and are an established marker of lipid oxidation during liver injury [181]. TNFα-treated Caco2 cells were either incubated with 0.5 μM PCA, 1 μM cyanidin-3-*O*-glucoside, 0.5 μM delphinidin-3-*O*-glucoside, 0.1 μM peonidin or 5 μg/mL anthocyanins [141]. All of the compounds significantly decreased 4-HNE-protein adducts below the TNFα-treated cells and some the control group [141]. In mice fed HFD and anthocyanins, ileal 4-HNE-protein adducts decreased to that of the control [141]. However, the control group that was fed anthocyanin did not differ from the control group without anthocyanins [141]. Mice fed a HFD supplemented with cyanidin and delphinidin decreased hepatic 4-HNE-protein adducts [142]. Based on findings from both pre-clinical (Table 1) and clinical studies (Table 2), the habitual consumption of anthocyanins appears to reduce the oxidation of lipids and proteins. Most effects are seen in populations/models with elevated oxidative stress/compromised antioxidant status. Reductions in lipid peroxidation may prevent atherosclerosis development in part through

Table 1
Antioxidant effects and regulation of redox state by anthocyanins in pre-clinical models.

Category	Parameter
Total Antioxidant Capacity	*TAC* (serum: ↑ in 3 studies [31,61,63]); *TAS* (serum: ↑ in 1 studies [62]); *TEAC* (serum: ↑ in 2 studies [59,64] hepatic: ↑ in 1 study [65]); *FRAP* (serum: ↔ in 2 studies [62,67]); *ORAC* (serum: ↔ in 1 studies [60]); *DPPH* (serum: ↑ in 1 study [60]); *ACW* (serum: ↑ in 2 studies [62,66]); *ACL* (serum: ↑ in 1 study [62])
Antioxidant Defense	*Nrf2 expression* (hepatic: ↑ in 1 study [118]); *NQO1 expression* (Hepatic: ↑ in 1 study [118]); *GPx* (Cell: ↑ in 1 study [105] ↔ in 1 study [107], Serum: ↑ in one study [104] ↔ in one study [111], Hepatic: ↑ in 10 studies [21,60,64,103,104,111–114,116] ↔ in 2 studies [59,107]); *GSH* (Cell: ↑ in 1 study [105], Hepatic: ↑ in 5 studies [21,60,112,116,118] ↔ in 2 studies [59,64]); *GST* (Hepatic: ↔ in 1 study [111], Intestinal: ↔ in 1 study [111]); *CAT* (Cell: ↑ in 3 studies [105–107], Serum: ↑ in 5 studies [31,60,103,111,123], Hepatic: ↔ in 6 studies [59,64,107,111–113], Intestinal: ↔ in 1 study [111]); *SOD* (Cell: ↑ in 3 studies [105–107], Serum: ↑ in 3 studies [31,103,104] ↔ in 1 study [111], Plasma: ↑ in 2 studies [66,114] ↔ in 1 study [67], Hepatic: ↑ in 7 studies [30,65,104,107,113,123,124] ↔ in 1 study [111], Intestinal: ↔ in 1 study [111]); *Mn-SOD (SOD2)* (Hepatic: ↑ in 2 studies [59,64] ↔ in 2 studies [107,112])
Oxidative Stress/ Inflammatory Signaling	*ROS production* (Cell: ↓ in 4 studies [78,106,107,139], Serum: ↓ in 1 study [112]); *Peroxynitrite levels* (Aortic: ↓ in 1 study [140]); *Nitrotyrosine levels* (Aortic: ↓ in 1 study [140]); *Superoxide formation* (Cell: ↓ in 4 studies [107,140], Aortic: ↓ in 2 studies [140,145], Cardiac: ↓ in 1 study [114], Thoracic: ↓ in 1 study [114]); *Mitochondrial superoxide levels* (Aortic: ↓ in 1 study [140]) *NO levels* (Cell: ↑ in 1 study [106], Hepatic: ↑ in 1 study [113], Aortic: ↑ in 1 study [140]); *NOS2* (Ileal: ↓ in 1 study [141]); *NOX1 expression* (Hepatic: ↓ in 1 study [141], Ileal: ↓ in 1 study [141]); *NOX3 expression* (Hepatic: ↓ in 1 study [142]); *NOX4 expression* (Cell: ↓ in 1 study [106], Hepatic: ↓ in 2 studies [141,142], Ileal: ↓ in 1 study [141]); *eNOS activity* (Cell: ↑ in 1 study [106]); *eNOS phosphorylation* (Cell: ↑ in 3 studies [140,143,144]); *iNOS expression* (Hepatic: ↓ in 1 study [118]) *NFκB activation* (Cell phosphorylation: ↓ in 1 study [141], Hepatic phosphorylation: ↓ in 1 study [142], Hepatic translocation: ↓ in 1 study [118], Hepatic DNA Binding: ↓ in 1 study [142]); *IKK phosphorylation* (Hepatic: ↓ in 1 study [142]); *ERK1/2 phosphorylation* (Cell: ↓ in 1 study [141]); *JNK phosphorylation* (Hepatic: ↓ in 1 study [142]); *COX2 expression* (Hepatic: ↓ in 1 study [118]); *HO-1 expression* (Hepatic: ↓ in 1 study [118])
Lipid/Protein/Lipoprotein Oxidation	*4-HNE protein adducts* (Cell: ↓ in 1 study [141], Hepatic: ↓ in 1 study [142], Ileal: ↓ in 1 study [141]); *AOPPs* (Serum: ↔ in 1 study [63], Hepatic: ↔ in 1 study [63], Colonic: ↔ in 1 study [63], Renal: ↓ in 1 study [63]); *Lipid peroxidation* (Aortic: ↓ in 1 study [145]); *MDA* (Serum: ↓ in 6 studies [31,103,104,113,166,168], Hepatic: ↓ in 8 studies [21,30,104,113,116,118,167,168], Renal: ↑ in 1 study [113], Brain: ↔ in 1 study [113], Aortic: ↓ in 1 study [140]); *TBARS* (Serum: ↓ in 8 studies [22,59,60,62,64,107,124,166], ↔ in 1 study [63], Hepatic: ↓ in 5 studies [60,61,112,118,170], ↔ in 2 studies [59,63], Renal: ↓ in 1 study [60], Brain: ↓ in 1 study [60], Colonic: ↔ in 2 studies [63]); *8-iso-PGF2-alpha* (Hepatic: ↔ in 1 study [111]); *Protein Carbonyl* (Hepatic: ↓ in 1 study [112]) *Cu-induced LDL oxidation* (LDL: ↓ in 5 studies [107,158–161]); *ApoB fragmentation* (LDL: ↓ in 1 study) [159]; *TBARS* (LDL: ↓ in 1 study [159]); *oxLDL* (Plasma: ↓ in 1 study [21], Serum: ↓ in 1 study [140], Serum susceptibility: ↓ in 1 study [22])

Abbreviations: ↑, increase; ↓, decrease; ↔ no change; TAC, total antioxidant capacity; TAS, total antioxidant; TEAC, trolox equivalent antioxidant capacity; FRAP, ferric reducing ability of plasma; ORAC, oxygen radical absorbance capacity; DPPH, 2,2-diphenyl-1-picryl-hydrazyl-hydrate; ACW, anti-radical capacity of water-soluble substances; ACL, anti-radical capacity of water-soluble substances; Nrf2, NF-E_2-related factor 2; NQO1, NAD(P)H quinone 1; GPx, glutathione peroxidase; GSH, glutathione; GST, glutathione; CAT, catalase; SOD, superoxide dismutase; SOD2, Mn-SOD; ROS, reactive oxygen species; NO, nitric oxide; NOS2, nitric oxide synthase 2; NOX1, NADPH oxidase 1; NOX3, NADPH oxidase 3; NOX4, NADPH oxidase 4; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; IKK, IκB kinase; ERK1/2, extracellular signal-regulated kinase ½; JNK, c-Jun-N-terminal-kinase; COX2, cyclooxygenase 2; HO-1, heme-oxygenase 1; 4-HNE, aldehyde 4-hydroxynonenal; AOPPs, antioxidant oxidation protein products; MDA, malondialdehyde; TBARS, thiobarbituric acid reactive substances; iso-PGF2-α, iso-prostaglandin 2 alpha; LDL, low-density lipoprotein; apoB, apolipoprotein B; oxLDL, oxidized LDL.

Table 2
Antioxidant effects of anthocyanins in clinical trials investigating cardiovascular disease.

Category	Parameter
Total Antioxidant Capacity	*TAC* (↑ in 5 studies [68–71,76] ↔ in 1 studies [171]); *TAS* (Postprandial serum: ↑ in 1 study [75], Urine: ↔ in 1 study [70]); *TEAC* (↔ in 1 study [77]); *FRAP* (↑ in 7 studies [26,68,72,73, 75,76,119] ↔ in 3 studies [15,278]); *ORAC* (↑ in 2 studies [73,75]); *DPPH* (↑ in 1 study [74]); *CAP-e* (↑ in 1 study [78])
Antioxidant Defense Enzymes	*GPx* (↑ in 2 studies [68,102], ↔ in 4 studies [69, 119,120,122]); *GSH* (↔ in 1 study [119]); *HDMD cellular GSH content* (↑ in 1 study [121]); *GST* (↔ in 1 study [122]); *CAT* (↑ in 2 studies [68,69], ↔ in 2 studies [119,120], ↓ in 1 study [102]); *SOD* (↑ in 4 studies [69,102,125,126] ↔ in 4 studies [68,119,120,122])
Oxidative Stress & Inflammation	*ROS levels* (↔ in 3 studies [70,148,149]); *Polymorphonuclear cell ROS levels* (↓ in 1 study [78]); *PBMC iNOS expression* (↑ in 1 study [147]); *Homocysteine* (↔ in 1 study [119])
Lipid/Protein/Lipoprotein Oxidation	*Serum lipid peroxidation* (↓ in 4 studies [74,78, 102,121,165]); *MDA* (Serum: ↓ in 4 studies [69, 73,75,92,169], Urine: ↔ in 2 studies [75,119]); *Serum TBARS* (↔ in 1 study [171]); *Postprandial serum TBARS* (↓ in 1 study [78]); *8-iso-PGF2-alpha* (Serum: ↓ in 3 studies [26,163, 174], ↔ in 2 studies [74,77], Urine: ↓ in 3 studies [73,126,173], ↔ in 1 study [174]) *Protein Carbonyl* (Serum: ↓ in 1 study [26]); *AOPPS* (Postprandial serum: ↓ in 1 study [172], Serum: ↓ in 1 study [179]); *oxLDL* (Serum:↓ in 4 studies [149,162,163,165], ↔ in 2 studies [71, 164])
Antioxidant and Atheroprotective Properties of HDL	*HDL particles* (serum: ↔ in 1 study [272]); *ApoA-I* (↑ in 2 studies [149,273] ↔ in 2 studies [179, 272]); *ApoC-III* (↓ in 1 study [26]); *CEC* (↑ in 2 studies [25,273] ↔ in 2 studies [179,272]) *PON1 arylesterase* (↑ in 3 studies [25,121,165], ↔ in 2 studies [179,272]); *PON1 lactonase* (↔ in 2 studies [179,272]); *MPO* (serum: ↔ in 1 study [179])

Abbreviations: ↑, increase; ↓, decrease; ↔ no change; TAC, total antioxidant capacity; TAS, total antioxidant; TEAC, trolox equivalent antioxidant capacity; FRAP, ferric reducing ability of plasma; ORAC, oxygen radical absorbance capacity; DPPH, 2,2-diphenyl-1-picryl-hydrazyl-hydrate; CAPe, cell-based antioxidant protection of erythrocyte; GPx, glutathione peroxidase; GSH, glutathione; GST, glutathione; CAT, catalase; SOD, superoxide dismutase; ROS, reactive oxygen species; iNOS, inducible nitric oxide; MDA, malondialdehyde; TBARS, thiobarbituric acid reactive substances; iso-PGF2-α, iso-prostaglandin 2 alpha; AOPPs, antioxidant oxidation protein products; oxLDL, oxidized LDL; apoA-I, apolipoprotein a-I; apo-CIII, apolipoprotein CIII; CEC, cholesterol efflux capacity; PON1, paraoxonase 1; MPO, myeloperoxidase.

reductions in oxLDL, while reducing protein oxidation products may alleviate the inflammatory burden in high oxidative stress conditions.

3. Regulation of atherosclerotic vasculature redox state by anthocyanins

3.1. Macrophage oxidative stress

Regulation of the redox state of cells found in the vasculature may protect against atherosclerosis. Macrophage oxidative stress plays a role in promoting an inflammatory microenvironment, which accelerates atherosclerotic plaque formation. Oxidative stress and lipid peroxidation increases expression of cell adhesion molecules leading to monocyte recruitment into the sub-endothelial space and further into the arterial intima by chemoattractant proteins such as MCP-1 [130]. Once inside, monocytes differentiate into macrophages that express scavenger receptors, including cluster of differentiation 36 (CD36) and lectin-type oxLDL receptor 1 (LOX1), to internalize modified/oxidized lipoproteins [130]. Monocyte derived macrophages also differentiate into M1 or M2 macrophages either exacerbating or protecting against oxidative stress, respectively [182]. OxLDL has also been shown to activate PPARγ upregulating the expression of vascular endothelial growth factor in macrophages after binding to LOX1 [183,184]. However, macrophages can accumulate an excess of lipids resulting in foam cell formation, a hallmark of early atherosclerotic lesion [130]. Overexpression of CD36 activates the pro-atherogenic role of Nrf2 facilitating the development of atherosclerosis [185]. Foam cell formation can also be promoted by the binding of oxLDL to C-reactive protein (CRP) [186]. Foam cells release proinflammatory cytokines prompting ROS generation and an inflammatory response which can lead to atheromatous plaques [130]. Disruption of the plaque can lead to thrombosis, obstructing blood flow, or plaque rupture [187]. As stated previously, NOX are major ROS generators, and their activity in macrophages are important in the formation of oxLDL, endothelial adhesion molecule secretion and monocyte infiltration [188]. NOX can be activated by oxLDL and consequently decreases eNOS activity [189]. Furthermore, activation of NOX prompts ERK1/2, MAPK, and NFκB pathways resulting in monocyte activation and macrophage proliferation [190]. Cigarette smoke exposure increases macrophage oxidative stress by increasing intracellular ROS [191]. In addition, macrophage cholesterol content increases and cholesterol efflux to HDL is inhibited [191]. In order to compensate, the expression of paraoxonase 2 (PON2), an antioxidant enzyme, is increased which attenuates proinflammatory macrophage activation and increases anti-inflammatory macrophage activation [191,192]. In addition, GSH levels increase and antioxidant defense enzymes like GPx and catalase are upregulated in macrophages in response to an inflammatory signal such as oxLDL [193]. HO-1 is highly expressed by macrophages in atherosclerotic plaques and can hinder NOX activity protecting against oxidative stress [96,194]. Since macrophages can play a pro- and anti-inflammatory role in the progression of atherosclerosis, it is important to identify if anthocyanins promote anti-inflammatory responses to protect against CVD.

Anthocyanins have been shown to attenuate macrophage oxidative stress by reducing oxLDL uptake, oxidative stress and increasing the antioxidant defense system (Table 3). As a result, anthocyanins reduce mRNA MCP-1 levels and also decrease M1-polarized macrophages, the proinflammatory phenotype [195,196]. In murine macrophages, anthocyanin-rich fractions increased Nrf2 expression [197–200], while TAC [198,201], SOD [198,200,202], CAT [202,203], GR [203], GPx [198,200], GSH [204] and HO-1 [198] also increased. In addition, anthocyanin-rich pomegranate juice increased PON2 expression [205] (via activator protein 1 (AP-1) and PPARγ activation), protein abundance [205], and lactonase activity [206]. Rozenberg et al. treated J774.1 macrophages with a pomegranate sugar-fraction which resulted in reduced total peroxide levels and PON2 lactonase activity compared to white grape juice sugars and the control [204]. On the other hand,

Table 3
Regulation of atherosclerotic vasculature redox state by anthocyanins in pre-clinical models.

Category	Parameter
Macrophage Antioxidant Defense, Oxidative Stress, Inflammation & Lipid Metabolism	*TAC* (↑ in 2 studies [198,201]); *Nrf2 expression* (↑ in 4 studies [197–200]); *SOD activity* (↑ in 3 studies [198,200, 202]); *CAT activity* (↑ in 2 studies [202, 203]); *GR activity* (↑ in 1 study [203]); *GPx activity* (↑ in 2 studies [198,200]); *GSH* (↑ in 1 study [204]); *HO-1 expression* (↑ in 1 study [198]); *PON activity* (arylesterase: ↔ in 1 study [208], lactonase: (↔ in 1 study [208]); *PON2 expression* (↑ in 1 study [205] ↓ in 1 study [204]); *PON2 protein abundance* (↑ in 1 study [205]); *PON3 expression* (↑ in 1 study [206]) *ROS production* (↓ in 7 studies [197,199, 200,202,209–212]); *Total macrophage peroxide* (↑ in 2 studies [121,204]); *TBARS* (↓ in 2 studies [201,214]); *MDA* (↓ in 1 study [198]); *Cellular lipid peroxide* (↓ in 1 study [206]) *NFκB activation* (phosphorylation: ↓ in 7 studies [199,200,212,217,219,223,224] and translocation: ↓ in 4 studies [197, 209,217,219]); *AP-1* (expression: ↓ in 2 studies [211,219]); *JNK1* (expression: ↓ in 3 studies [210,211,219]); *ERK1* (expression: ↓ in 2 studies [210,212]); *COX2 expression* (↓ in 8 studies [197, 199–201,210,217–219]); *Prostaglandin E2 secretion* (↓ in 2 studies [210,220]); *iNOS expression* (↓ in 6 studies [197,200, 211,217,219,221]); *NOX1 expression* (↓ in 1 study [197]) *Cellular lipid accumulation* (↓ in 1 study [214]); *Cholesterol biosynthesis* (↓ in 1 study [213]); *Foam cell formation* (↓ in 1 study [159,214]); *oxLDL uptake* (↓ in 4 studies [159,206,213,214]); *CD36* (mRNA and protein: ↓ in 1 study [214]); *PPARγ* (protein: ↓ in 1 study [214] ↑ in 1 study [215]); *oxLDL-induced cell apoptosis* (Capase-3: ↓ in 2 studies [158,204])
Endothelial Cell Antioxidant Defense, Oxidative Stress, & Inflammation	*Nrf2* (expression: ↓ in 1 study [238]); *GSH* (↑ in 2 studies [238,239]); *GSH/GSSG* (↑ in 1 study [238]); *Oxidized GSH* (↓ in 1 study [238]); *SOD* (activity: ↑ in 1 study [238], protein: ↑ in 1 study [108], production: ↑ in 1 study [240]); *HO-1* (expression: ↑ in 1 study [238] protein: ↑ in 1 studies [108,240]) *ROS levels* (↓ in 6 studies [108,140,143, 239,240,242]); *NO levels* (↑ in 4 studies [140,242,245,251], iNOS-derived NO ↔ in 1 study [247]); *Peroxynitrite levels* (↓ in 1 study [140]); *Nitrotyrosine levels* (↓ in 1 study [140]); *NOX1 expression* (↓ in 1 study [143]) *NOX4 expression* (↓ in 3 studies [108,143,242]); *iNOS expression* (↓ in 2 studies [143,244]); *eNOS* (phosphorylation: ↑ in 1 study [140], aortic phosphorylation: ↑ in 1 study [145], expression: ↑ in 1 study [245], activity: ↑ in 1 study [246]); *XO activity and protein abundance* (↓ in 1 study [240]) *NFκB nuclear translocation* (↓ in 3 studies [238,248,252]); *ERK1/2* (expression: ↓ in 1 study [238]); *COX2 expression* (↓ in 1 study [239]); *Glycated LDL-induced ER stress* (↓ in 1 study [237]); *Apoptosis* (↓ in 1 study [243]); *Endothelial dependent relaxation* (↑ in 2 studies [140,145]); *Vascular tension* (↑ in 1 study [140])
Antioxidant and Atheroprotective Properties of HDL	*ApoA-I* (serum: ↔ in 1 study [170], intestinal expression: ↓ in 1 study [170]); *HDL/apoA-I* (serum: ↔ in 1 study [170]); *LCAT expression* (Hepatic: ↑ in 1 study [170]); *CEC* (↑ in 1 study [274]); *ABCA1-dependent cholesterol efflux* (↑ in 1 study [252]) *PON1 promoter activity* (Cell: ↔ in 1 study [208]); *PON1 arylesterase activity* (Cell: ↔ in 1 study [208], serum: ↑ in 3 studies [111,170,274], plasma: ↑ in 1 study [114])); *PON1 lactonase activity* (Cell: ↔ in 1 study [208], serum: ↑ in 1 study [274]); *PON1* (hepatic expression: ↑ in 1 study [170], ↔ in 1 study [274], hepatic protein: ↔ in 2 studies [170,274])

Abbreviations: ↑, increase; ↓, decrease; ↔ no change; TAC, total antioxidant capacity; Nrf2, NF-E_2-related factor 2; SOD, superoxide dismutase; CAT, catalase; GR, glutathione reductase; GPx, glutathione peroxidase; GSH, glutathione; HO-1, heme-oxygenase 1; PON, paraoxonase; TBARS, thiobarbituric acid reactive substances; MDA, malondialdehyde; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; AP-1, activator protein-1; JNK, c-Jun-N-terminal-kinase; ERK1/2, extracellular signal-regulated kinase ½; COX2, cyclo-oxygenase 2; iNOS, inducible nitric oxide synthase; NOX1, NADPH oxidase 1; oxLDL, oxidized LDL; CD36, cluster of differentiation 36; PPAR, peroxisome proliferator-activator receptor; GSSG, oxidized glutathione; NO, nitric oxide; eNOS, endothelial nitric oxide synthase; XO, xanthine oxidase; ER, endoplasmic reticulum; apoA-I, apolipoprotein a-I; ABCA1, ATP-binding cassette transporters sub-family A member 1; LCAT, lecithin-cholesterol acyltransferase; CEC, cholesterol efflux capacity.

while PON2 increases, PON3 decreases in macrophages during states of oxidative stress [207]. Pomegranate juice also decreases total peroxide levels [121,206] and increases PON3 expression [207]. However, anthocyanins (cyanidin-3-glucoside and delphinidin-3-glucoside) and its metabolites (PGA, PCA, ferulic acid, and 4-hydroxybenzaldehyde) at a concentration of 1 μM and 10 μM did not alter PON1 arylesterase or lactonase activity in PON1-Huh7, a liver hepatoma cell line [208]. Regardless, anthocyanin supplementation effectively decreased ROS production [197,199,200,209–212] and total macrophage peroxide [121]. Lee et al. observed that anthocyanins from blueberry, blackberry, and blackcurrant only decreased ROS levels in bone marrow-derived macrophages from Nrf2 wild-type mice, but not Nrf2-knockout mice [209]. This indicates that anthocyanins mediate macrophage ROS in a Nrf2-dependent manner. Alvarez-Suarez et al. treated RAW264.7 macrophages with Capuli cherry extract ranging from 5 to 50 μg/mL which resulted in a strong dose dependent reduction in ROS production [202]. In addition, foam cell formation decreases in response to anthocyanins due to decreased oxLDL uptake and decreased cholesterol biosynthesis [121,159,213,214] via downregulation of CD36 mRNA and protein and PPARγ protein [214]. Although Xia et al. found that anthocyanins can induce PPARγ, this increase did not attribute to foam cell formation [215]. As a consequence of decreased LDL uptake, TBARS, MDA, cellular lipid peroxide and lipid accumulation were also reduced [121,198,201, 214]. Anthocyanins also inhibited oxLDL-induced cell apoptosis via decreased full length Caspase-3 [158,204]. COX2, an enzyme highly expressed in atherosclerotic lesions and induced by proinflammatory cytokines, can advance the formation and secretion of prostaglandins [216]. Anthocyanins have been shown to decrease COX2 expression [197,199–201,210,217–219] and thus prostaglandin production and secretion were diminished [210,220]. Furthermore, COX2 may interact with iNOS [216], whose expression was also decreased after anthocyanin treatment [197,200,211,217,219,221]. Even more, NO levels [199–201,210,211,217,218,220–222], and the activation and expression of NOX1 decreased [197]. Ultimately, anthocyanins protect macrophages against oxidative stress by mitigating phosphorylation [199,

200,212,217,219,223,224] and translocation [197,209,217,219] of NFκB as well as toll-like receptor (TLR4) dimerization inhibiting TLR4/myeloid differentiation factor 2-dependent NFκB activity [223]. In addition, anthocyanins exerts its anti-inflammatory effects by decreasing the activation of the AP-1 [211,219], and MAPKs, JNK1 [210,211,219] and ERK1 [210,212], pathways.

3.2. Endothelial cell oxidative stress

Oxidative stress also affects the endothelium of the vessel walls, which plays a crucial role in the development and progression of atherosclerosis. The endothelium is a layer of endothelial cells in the inner portion of the vessel wall that can regulate molecular transport as well as vascular tone [225,226]. It is also involved with smooth muscle cell proliferation and migration, thrombogenesis and fibrinolysis [227]. Therefore, endothelial dysfunction can progress the atherosclerotic process. CRP has been shown to induce superoxide production in human aortic endothelial cells (HAECs) [228] and inhibit endothelial cell NO production therefore contributing to endothelial dysfunction [229]. NO production promotes vasodilation, vasoprotection and prevents atherosclerosis [230]. NO reduces proliferation of arterial wall smooth muscle cells and prevents plaque formation by reducing monocyte stickiness [231]. In addition, oxLDL can bind to CRP activating the complement system initiating further inflammatory responses [232]. ROS and RNS, mainly produced by NOX, attack endothelial cells compromising their function [233,234]. Endothelial cells also have eNOS that produce protective NO from L-arginine using tetrahydrobiopterin (BH_4) as a cofactor. If the availability of either the reactant and/or the cofactor are diminished, eNOS uncouples producing a superoxide anion instead of NO [235]. During states of oxidative stress, endothelial function is further compromised as the increase in superoxide anions can stimulate its combination with NO to form peroxynitrite, which can oxidize BH_4 [236]. As a consequence, endothelial NO bioavailability remains low, reducing endothelial protection. Expression of Nrf2 reduces oxidative stress which affects vascular smooth muscle cell proliferation, migration and inflammation [99].

Anthocyanin treatment in endothelial cells has been reported to increase antioxidant defense enzymes, decrease ROS, and, therefore, improve endothelial function (Table 3). As an example, anthocyanin-rich Saskatoon berries inhibited glycated LDL-induced endoplasmic reticulum (ER) stress in human umbilical vascular endothelial cell (HUVEC) cells [237]. The Nrf2 pathway is activated in HUVECs treated with cyanidin-3-*O*-glucoside which induces ERK1/2 independent of TNFα exposure [238]. In response, GSH levels increase as oxidized glutathione (GSSG) decreases improving the GSH/GSSG ratio [238,239]. In addition, XO [240] is downregulated, while SOD activity [238,240] and HO-1 mRNA [108,238,240] increased after anthocyanin treatment. HO-1 has been shown to be upregulated during states of oxidative stress although protective towards atherosclerosis. HO-1 in HAECs diminishes monocyte oxLDL-dependent chemotaxis [241]. As a result, anthocyanin treated HUVECs and aortic endothelial cells resulted in diminished ROS levels [108,140,143,239,240,242], and inhibited apoptosis [243]. In addition, NOX1 [143], NOX4 [108,143,242], iNOS [143,244], and COX2 [239] expression significantly decreased after anthocyanin supplementation whereas eNOS phosphorylation [140], expression [245], and activity increased [246]. As a result, peroxynitrite and nitrotyrosine levels decreased [140] and NO levels increased [140,242,245]. Although one study found that specifically iNOS derived NO was not altered in monocyte derived macrophages [247]. Accordingly, anthocyanins mitigated NFκB nuclear translocation [238,248]. Due to the ability of anthocyanins to increase NO bioavailability, endothelial dependent relaxation is enhanced [140,145]. Mulberry extract-treated aortic rings from HFD-fed mice resulted in a dose-dependent increase in vascular tension [140]. Interestingly, anthocyanin intake associated with lower arterial stiffness in women [249]. In addition, endothelial cells express ATP-binding cassette transporters sub-family G member 1 (ABCG1), which effluxes cholesterol and 7-oxysterols maintain endothelial function [250]. Anthocyanin supplementation in apoE$^{-/-}$ mice increased ABCG1 expression [145]. Furthermore, ABCG1 flux of oxysterols has also been reported to induce NO synthesis in the endothelium and activate LXRα in HAECs [251]. Lastly, in HK-2 cells, an endothelial cell line, anthocyanins reduced Liver X receptor alpha (LXRα)-associated NFκB nuclear translocation and activated PPARα-LXRα-ATP-binding cassette transporters sub-family C member 1 (ABCA1)-dependent cholesterol efflux [252].

3.3. Effects on antioxidant properties of HDL

Anthocyanin intake has been reported to influence HDL metabolism and function in pre-clinical and clinical models (see Millar et al. for review) [253]. HDL is an antiatherogenic lipoprotein found in low levels in diseased populations [254]. HDL's major function is RCT, where HDL is lipidated with cholesterol effluxed from extrahepatic tissues and subsequently returns to the liver targeting the cholesterol for biliary excretion after binding to scavenger receptor class B type 1 (SR-B1) [255]. Apolipoprotein A-I (apoA-I) is structural component of HDL which acts as a ligand for SR-B1, lecithin-cholesterol acyltransferase (LCAT) and the ABC transporters activities, and whose modification can result in poor HDL interactions and subsequently affect RCT efficiency. The antioxidant activity that is attributed to HDL is thought to be primarily due to the presence of apoA-I, as well as antioxidant enzymes PON1 and platelet activating factor acetyl hydrolase [256]. Several other apolipoproteins (apo E, J, A-IV) present on HDL may possess antioxidant activity as well [257]. HDL is able to remove oxidizable lipid species from LDL, rendering it resistant to oxidation [258]. The removal of these seeding molecules involved in oxidation was attributed to apoA-I and PON-1 on HDL [258]. In addition to its role in RCT, HDL has been proposed to also possess antioxidant, anti-inflammatory, anti-thrombotic, and anti-apoptotic properties [253]; some have probably yet to be discovered. HDL can exhibit antioxidant effects by preventing LDL oxidation *in vivo* [259]. Lipid hydroperoxides produced on LDL can migrate towards the hydrophobicity of HDL's cell surface and can be transferred directly or via lipid transfer proteins [260]. HDL interferes with the glycation of LDL and can accumulate oxidized lipids from triglyceride-rich remnant particles and endothelial cells [110]. Interestingly, HDL lipid peroxide levels remain unchanged due to HDL's ability to metabolize these lipid hydroperoxides; delaying LDL oxidation by preventing their accumulation mediated by PON1 [261,262]. PON1 is an enzyme produced by the liver that circulates on HDL and has been independently inversely associated with coronary events [263,264]. However, in chronic states of inflammation, HDL particles can become impaired and its membrane components can undergo oxidation, as commonly seen in CVD. This is comprised of an increase in particle free cholesterol, triglycerides, and a reduction in PL content which has been associated with impaired efflux [265,266]. MPO is a pro-oxidant enzyme whose activity is commonly elevated in states of systemic inflammation [267], where it oxidizes HDL impairing its capacity to protect the endothelium [8]. These lipid peroxides residing on the surface of the particle can decrease the cholesterol-accepting capacity of HDL itself, or be transferred to LDL or very low-density lipoprotein (VLDL), which can be detrimental for those lipoproteins as well [255]. It has also been reported that MPO can oxidize apoA-I, and subsequently impair HDL function by impaired binding [95]. Furthermore, when PON1 activity is impaired, concentrations of MDA, a well-established marker of oxidative stress, are increased [268].

HDL functionality and antioxidant capacity are critical for protection against CVD and can be measured by several assays such as HDL-associated lipid peroxides and measures of PON1 activity. Measures of oxLDL, PON1 activity, or oxidized PLs can provide insight on the antioxidant capacity of HDL [269]. One method, as described by de Juan-Franco, measures HDL's antioxidant capacity through the lag phase change in conjugated diene formation and electrophoretic

mobility of LDL [270]. Furthermore, NO production and cytokine production upon addition of HDL can be measured to evaluate the vasoprotective or anti-inflammatory roles of HDL [269]. HDL can induce eNOS activation, releasing NO, resulting in vasorelaxation via SR-B1 and apoA-I binding [271]. There is strong evidence that anthocyanin improves markers associated with HDL and HDL function. Although, in MetS patients grape and agraz consumption did not affect HDL particle concentrations [272], serum MPO concentrations [179], apoA-I concentrations [179,272], blueberries and anthocyanin consumption increased apoA-I levels in at risk populations [149,273]. However, grape and agraz consumption in individuals with MetS did not alter apoA-I concentrations [179,272]. In apoE$^{-/-}$ mice fed 1.25% (w/w) black elderberry extract for 6 weeks, serum apoA-I and HDL/apoA-I ratio were not affected [170]. However, apoA-I expression was increased in the small intestine [170]. Similarly, hepatic expression of ABCA1, the transporter required for efflux of cholesterol to lipid-poor HDL, tended to decrease while that of LCAT was increased [170,274]. Conversely, apoC-III, which inhibits lipoprotein lipase (LPL) resulting in triglyceride-rich lipoproteins including HDL [275,276], was decreased in diabetic patients after 24 weeks of daily 160 mg anthocyanin supplementation [26]. Chokeberry consumption (50 mg/kg/day) in HFD-fed mice decreased hepatic LPL expression after 12 weeks [65]. There is a plethora of evidence that suggest anthocyanins increase PON1 activity and expression. In contrast, anthocyanins did not modulate PON1 promoter activity or PON1 arylesterase and lactonase activity in PON1-Huh7 cells [208]. Several preclinical trials resulted in increases in PON1 serum activity and hepatic mRNA expression [111,114,170,274]. In addition, an increase in PON1 arylesterase activity was positively correlated with HDL cholesterol efflux capacity (CEC) [274]. In MetS patients, PON1 activity remained unaffected [179,272], while in hypercholesterolemic patients PON1 increased after anthocyanin supplementation [25]. This increase was inversely correlated with lipid hydroperoxide levels [25]. Surprisingly, pomegranate juice consumption increased PON1 after 3 months in diabetic patients and after 1 year in atherosclerotic patients [121,165]. Some of the patients with atherosclerosis continued to consume pomegranate juice for 2 more years which did not further increase PON1 expression but the initial increase was maintained [165]. Increased PON1 activity promotes macrophage CEC via upregulated ABCA1 [259], therefore it is logical that anthocyanin intake also improves CEC in pre-clinical and clinical models. ApoE$^{-/-}$ mice fed 0.25% and 1% black elderberry extract for 24 weeks exhibited increased CEC [274]. In dyslipidemic individuals anthocyanin supplementation increased cholesterol efflux capacity [25,273] although, CEC was not altered in MetS patients [179,272]. As for the mechanism behind the increase in efflux capacity most studies report some enhancement through LXRα [215,252,277], which happens to be upstream of ABCA1. Thus, anthocyanins appear to increase the antioxidant capacity of HDL across the various animal and clinical models (Tables 2 and 3). Intake of anthocyanin-rich foods may improve HDL function via increased apoA-I, ABCA1, and PON1 expression therefore increasing cholesterol efflux capacity.

4. Conclusions

The consumption of anthocyanins increases total antioxidant capacity, antioxidant defense enzymes, and HDL antioxidant properties by several measures in preclinical and clinical populations. Anthocyanins appear to impart their antioxidant actions via direct and indirect mechanisms. Anthocyanins and their metabolites can promote intracellular Nrf2 activation and antioxidant gene expression. As a result, antioxidant defense enzymes such as SOD, CAT and GPx are upregulated in preclinical models. Results are mixed in clinical populations although most evidence suggests a protective effect by increasing activities of antioxidant defense enzymes. It is possible that beneficial effects are seen in preclinical populations due to supraphysiological concentrations. Future clinical trials should increase anthocyanin concentrations of parent and bioactive metabolites to achieve increased anthocyanin efficacy. These actions counter oxidative stress and inflammatory signaling in cells present in atherosclerotic plaques, including macrophages and endothelial cells. Consumption of anthocyanins protects against oxidative stress in macrophages and endothelial cells in preclinical studies, through inhibiting NOX and iNOS while activating eNOS, resulting in enhanced NO bioavailability and improving endothelial function. Consequently, NFκB activation and nuclear translocation, and ROS levels may be reduced after consumption. Anthocyanins also tend to increase the antioxidative properties of HDL, including antioxidant apolipoproteins and via antioxidant enzyme activity. Anthocyanins may decrease serum oxLDL concentrations and oxLDL uptake, inhibiting foam cell formation. These effects on HDL may explain reductions in LDL oxidation and improvements in RCT (via CEC measure) seen in clinical studies. Overall, data suggest that anthocyanins can be protective through upregulating antioxidant defense systems and increasing the antioxidant capacity of HDL, while also decreasing lipid/protein oxidation and oxidative stress. In summary, anthocyanins may protect against atherosclerosis and cardiovascular disease through their effects on cellular antioxidant status and inflammation; however, their underlying mechanisms of action appear to be complex and require further elucidation.

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