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Review article

Mechanisms of flavonoid protection against myocardial ischemia–reperfusion injury

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ABSTRACT

Flavonoids have long been acknowledged for their unique antioxidant properties, and possess other activities that may be relevant to heart ischemia–reperfusion. They may prevent production of oxidants (e.g. by inhibition of xanthine oxidase and chelation of transition metals), inhibit oxidants from attacking cellular targets (e.g. by electron donation and scavenging activities), block propagation of oxidative reactions (by chain-breaking antioxidant activity), and reinforce cellular antioxidant capacity (through sparing effects on other antioxidants and inducing expression of endogenous antioxidants). Flavonoids also possess anti-inflammatory and anti-platelet aggregation effects through inhibiting relevant enzymes and signaling pathways, resulting ultimately in lower oxidant production and better re-establishment of blood in the ischemic zone. Finally, flavonoids are vasodilatory through a variety of mechanisms, one of which is likely interaction with ion channels. These multifaceted activities of flavonoids raise their utility as possible therapeutic interventions to ameliorate ischemia–reperfusion injury.

Contents

1. Introduction

Myocardial ischemia–reperfusion injury occurs following partial or complete cessation of blood circulation to the myocardium. Pathological alterations underlying ischemia–reperfusion injury begins during ischemia by stoppage of anaerobic metabolism which activates glycolysis, resulting in a decline in intracellular pH and consequently elevation of sodium and calcium in the cytosol [1,2]. With reperfusion, the ionic disturbances including calcium overload in the cytosol and mitochondria are exacerbated and production of superoxide and other reactive species of oxygen is intensified, leading eventually to structural and functional changes in cellular biomolecules and activation of signaling pathways that in severe cases result in cell demise [3,4].

Increased production of reactive oxygen species (ROS) and accumulation of calcium in the cytosol and mitochondria are two major causative factors of ischemia–reperfusion injury [5,6]. ROS mostly originate from three sources: the mitochondrial electron transport chain of myocytes [7,8], NADPH oxidase and myelope-

Abbreviations: AP-1, activator protein-1; eNOS, endothelial nitric oxide synthase; ICAM, intercellular adhesion molecules; IL, interleukin; MMP, matrix metalloproteinases; NF-κB, nuclear factor-kappa B; $NO^{\cdot}$, nitric oxide; NOS, nitric oxide synthase; $O_2^{\cdot-}$, superoxide; ROS, reactive oxygen species; TNF-α, tumor necrosis factor; VCAM, vascular cell adhesion molecules.

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roxidase of neutrophils [9,10], and xanthine oxidase of endothelial cells, although the contribution of xanthine oxidase in reperfusion injury of human hearts is a matter of debate [8,11–13]. Calcium overload is the result of ionic derangements starting after diminution of intracellular pH during ischemia [1,2]. Calcium overload not only by itself can initiate signaling pathways towards the injury, but it also accelerates formation of ROS and exacerbates destructive effects of ROS on cellular compartments and pathways [14,15].

Upon reperfusion of an ischemic tissue, a burst of ROS generation occurs due to rebound hyperoxia and oxidation of reduced intermediates [16,17]. Primary sources of ROS in this acute phase are likely the mitochondrial respiratory chain and xanthine oxidase. There is also a delayed and amplified generation of ROS due to the inflammatory response initiated by cytokines released from the damaged cells [18]. Each of these phases presents opportunities for flavonoids to intervene and help salvage the ischemic-reperfused tissue.

Flavonoids are a subgroup of the more extended family of polyphenols. More than 5000 flavonoids have been identified, each with a basic structure containing two benzene rings with a pyrane ring in the middle [19]. Flavonoids are outstanding antioxidants, at least *in vitro* [20], and because of their antioxidant activity as well as their abundance in fruit and vegetables they may partly contribute to the currently-known health benefits of plant foods [21]. There is ample evidence indicating beneficial effects of flavonoids on ischemic-reperfused hearts in *in vitro* applications (added to perfusate) or administered to blood [22–27], which could be of use in acute ischemia–reperfusion situations such as heart surgeries and transplants. There is also growing evidence that oral administration of flavonoids could provide protection against myocardial ischemia–reperfusion [28–36], which would be of benefit to people with chronic conditions such as ischemic heart disease. In this review, we have presented the possible mechanisms of cardioprotective effects of flavonoids that help the heart to overcome stress conditions of ischemia and reperfusion.

2. Antioxidant capacities

The most well-known protection of flavonoids from ischemia–reperfusion injury is conferred by their direct antioxidant activities. Nevertheless, there are other antioxidant effects that are delivered through different mechanisms such as post-translational modulation of enzymes and induction of genes (Fig. 1).

Although the mechanisms involved are uncertain, there is evidence that flavonoids inhibit ROS generation during heart ischemia–reperfusion. For example, 3 weeks feeding with grape seed proanthocyanidins decreased the electron spin resonance-detectable generation of free radicals during the initial minutes of reperfusion [37]. Furthermore, flavonoids have been shown to decrease ischemia–reperfusion-induced oxidative damage in myocardium. For instance, perfusing hearts with quercetin for 30 min and more strongly oral treatment with quercetin for 1 week before ischemia reduced malondialdehyde levels in heart tissues after reperfusion [32]. Similarly, 30 days feeding rats with either skin or flesh of red grapes attenuated formation of malondialdehyde in ischemic-reperfused hearts [38].

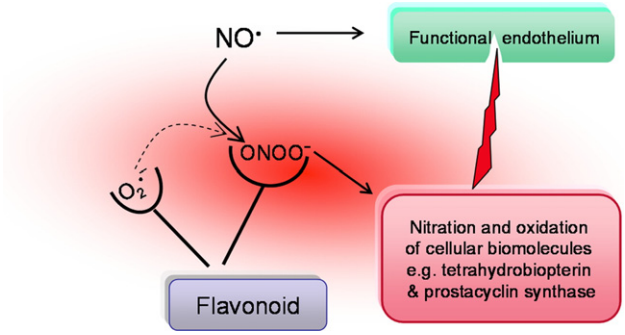

Fig. 2. Flavonoid scavenging of superoxide and peroxynitrite. Through scavenging superoxide, flavonoids improve $NO^{\cdot}$ bioavailability and inhibit peroxynitrite formation. Flavonoids can also scavenge peroxynitrite which damages endothelium and impairs endothelium-mediated vasorelaxation, leading ultimately to better blood circulation in coronary arteries. $O_2^{\cdot-}$, superoxide; $ONOO^{-}$, peroxynitrite.

2.1. Reactive oxygen species scavenging activities

Flavonoids may protect heart from ischemia–reperfusion injury by scavenging ROS. Flavonoids are potent scavengers of reactive species such as superoxide [39,40], peroxyl radicals [41,42], and peroxynitrite [43]. By scavenging such reactive species, flavonoids prevent formation of highly reactive species of oxygen and limit perpetuation of oxidative reactions. Moreover, scavenging ROS bestows additional benefits. For instance, by scavenging superoxide radicals the bioavailability of nitric oxide ($NO\cdot$) increases [44–47] and endothelial function in post-ischemic hearts improves (Fig. 2). Also, peroxynitrite is a highly reactive species of oxygen involved in cardiac reperfusion injury [48–50]. Peroxynitrite can cause

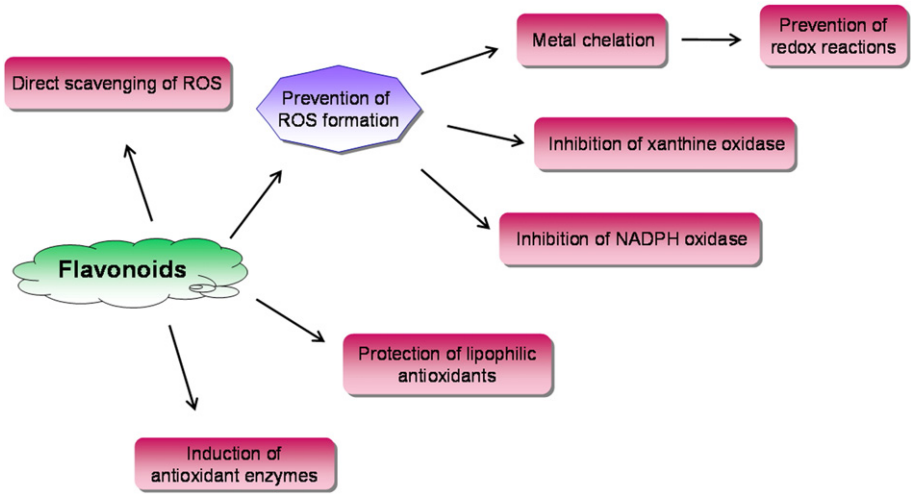

Fig. 1. Mechanisms of antioxidant effects of flavonoids. Flavonoids may exert their antioxidant effects by preventing generation of ROS, direct scavenging of ROS, or indirectly through enhancement of cellular antioxidant enzymes.

endothelium dysfunction through nitration of the nitric oxide synthase (NOS) cofactor, tetrahydrobiopterin, which in turn uncouples NOS and produces more ROS, and also through nitration and inhibition of prostacyclin synthase [51,52]. Thus, scavenging superoxide and peroxynitrite by flavonoids may help prevent endothelial dysfunction during reperfusion.

With regard to heart ischemia–reperfusion a major question is whether flavonoids or their metabolites reach heart tissues in sufficient quantities to be competitive scavengers of ROS, especially if delivered in the diet. The bioavailability of flavonoids is relatively low, and whether they reach biologically active levels *in vivo* has been questioned [53–55]. Vitamin C and glutathione in the aqueous phase and vitamin E in the lipid phase are likely to be much more important as direct scavengers of ROS. Nevertheless, flavonoids at nanomolar concentrations are sometimes found to protect cultured cells against reactive species such as peroxynitrite [e.g. 56]. Dietary supplementations with flavonoids have been shown to inhibit LDL oxidation in both *in vivo* and *ex vivo* settings [57–59]. However, it is difficult to ascertain if these effects are from direct scavenging of ROS or from other mechanisms. The levels of flavonoids that are achievable in heart tissues are not well known, although quercetin metabolites have been found deposited in human aorta [60]. Flavonoids at relatively low concentrations may become important antioxidants in microenvironments that are less accessible to vitamin C and vitamin E, such as at the interface of membranes [61].

2.2. Metal chelation

Some of the antioxidant effects of flavonoids are delivered through chelation of metal ions such as iron and copper [62–65]. Transition metal ions are critical co-factors of the Fenton reaction, and therefore their chelation by flavonoids makes them unavailable for this kind of reaction [66,67]. Decompartmentalization of iron has been found to be an important contributor to oxidative stress in heart ischemia–reperfusion injury [68,69]. This iron-initiated damage could be inhibited by perfusing hearts with desferrioxamine [70] or the flavonoid catechin [71]. Interestingly, it has been suggested that specific flavonoids upon binding metals may behave as a superoxide dismutase, scavenging superoxide more potently than the parent flavonoids while devoid of catalytic activity for the Fenton conversion of hydrogen peroxide to hydroxyl radicals [72–73]. Flavonoids may bind metals in metal:flavonoid ratios of 1:1, 1:2, 2:2, and 2:3 [74].

2.3. Inhibition of xanthine oxidase

Inhibition of xanthine oxidase may be one of the mechanisms by which flavonoids at physiological concentrations can mitigate ischemia–reperfusion injury. Several flavonoids including luteolin, apigenin, quercetin, myricetin, and kaempferol have been shown to inhibit xanthine oxidase [75–78]. Catechin did not inhibit xanthine oxidase activity [75,76]. However, there is conflicting evidence on catechins as tea leaves, which are known sources of catechins, inhibited xanthine oxidase activity to a greater extent than onions and apples, which are good sources of quercetin [79]. Particularly in coronary vessels and interstitial cells where xanthine oxidase activity is thought to participate in ischemia–reperfusion injury [80], inhibiting xanthine oxidase may help prevent formation of superoxide ($O_2^{\cdot-}$).

2.4. Inhibition of NADPH oxidases

NADPH oxidases are membrane-associated enzymes which catalyze transfer of one electron from NADPH to O_2 with consequent generation of $O_2^{\cdot-}$ [81,82]. Although NADPH oxidase was originally thought to be a neutrophil enzyme, recent investigations showed expression of NADPH oxidases in cardiovascular cells, including cardiac cells, endothelial and smooth muscle cells, and fibroblasts.

The expression of subunits [83] and the enzyme activity [84] of NADPH oxidase has been shown to increase in infarcted myocardium and failing hearts, and may contribute to ventricular remodeling and cardiac hypertrophy [85]. Nevertheless, the implication of NADPH oxidases in reperfusion injury and especially myocardial infarction is still subject to debate, with some reports showing an involvement [85–88] and others rejecting it [89–91]. It is worthwhile to note that although inhibiting NADPH oxidases may attenuate myocardial infarction damage [86], NADPH oxidases likely bring benefits to ischemic myocardium by promoting myocardial angiogenesis [92].

Although not yet investigated for this mechanism in ischemia–reperfusion, flavonoids have shown ability to suppress enzyme activity and/or expression of NADPH oxidases in other types of stress. For instance, epigallocatechin gallate inhibited expression of NADPH oxidase subunits in neonatal rat cardiomyocytes induced by angiotensin II and in rat hearts subjected to pressure overload [93]. Similarly, dietary administration of anthocyanins, proanthocyanidins, or catechin oligomers for 6 weeks lowered cardiac NADPH oxidase expression in rats treated with high-fructose diet [94]. Likewise, diminished activity of NADPH oxidase was observed in neutrophils of hemodialysis patients who consumed concentrated red grape juice for two weeks [95]. Interestingly, inhibition of the NADPH oxidase of endothelial cells has recently been proposed as a mechanism by which catechins improve vascular function [96], which could be of benefit in protecting against ischemia–reperfusion injury.

2.5. Reinforcement of cellular antioxidants

Human studies have shown depletion of non-enzymatic antioxidants such as glutathione, ascorbic acid, and vitamin E following myocardial ischemia–reperfusion [97]. Hydrophilic antioxidants, such as ascorbate and glutathione, have shown to work at the front line of defense against oxidative stress, protecting lipophilic antioxidants such as ubiquinol and vitamin E from oxidation [98]. Ascorbic acid also helps to regenerate vitamin E from its oxidized form [99], and is in turn recycled by glutathione [100], although vitamin C is also needed for the recovery of glutathione from its oxidized form [101]. In such a network, flavonoids are proposed to act as intermediate antioxidants, protecting lipophilic antioxidants and being protected by hydrophilic antioxidants [102,103]. The extent to which flavonoids may preserve other antioxidants in heart ischemia–reperfusion has not yet been documented.

2.6. Induction of phase 2 enzymes

The antioxidant effect of flavonoids and other phytochemicals may be exerted indirectly through induction of phase 2 enzymes [104–107]. Phase 2 enzymes are proteins whose expression is coordinately regulated by an antioxidant response element (ARE) located in the promoter region of the corresponding genes [108]. Since phase 2 enzymes are committed to neutralization and detoxification of xenobiotics and electrophiles, inducers of such genes may deliver protection against oxidative stress [109]. One of the phase 2 enzymes, heme oxygenase-1, has been recognized as an important mediator of the delayed phase of ischemia preconditioning [110], and its overexpression has led to reduced ventricular remodeling and hypertrophy [111] and better myocardial recovery and contractile function [112].

Over the last decade, a large number of investigations have indicated the ability of flavonoids to induce phase 2 enzymes in animals [113–116] and human cell cultures [117]. This ability of epigallocatechin gallate has recently been reviewed [118]. However, whether flavonoids can induce phase 2 enzymes in heart and thereby

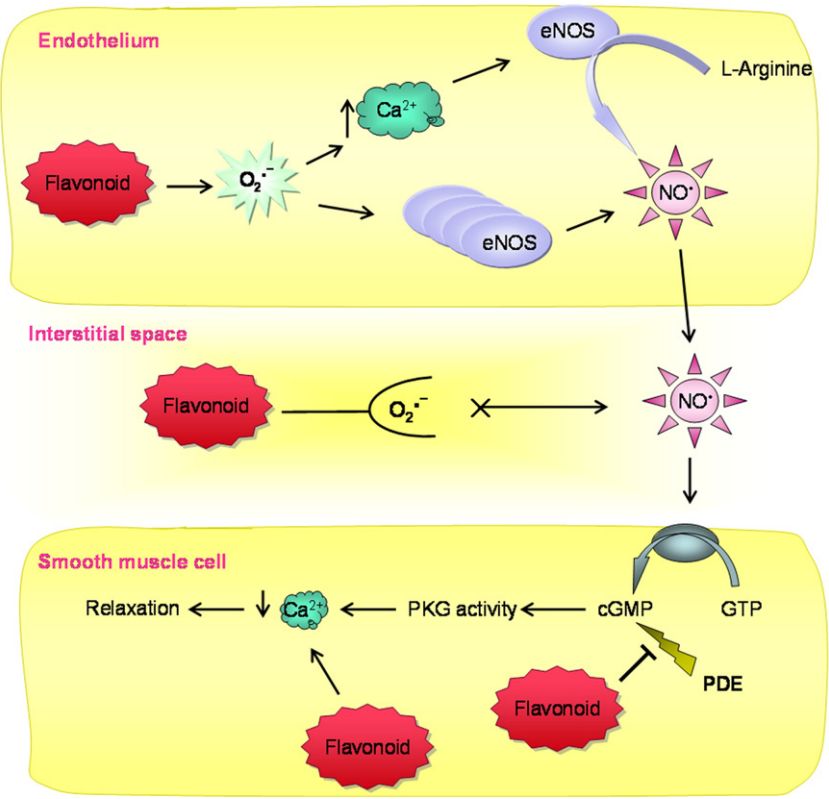

Fig. 3. Effect of flavonoids on endothelium-dependent vasorelaxation. Mild generation of $O_2^{\cdot-}$ by flavonoids is likely responsible for induction of eNOS as well as a mild increase of cytosolic Ca^{2+} as a cofactor for eNOS activation. Also, through scavenging $O_2^{\cdot-}$ in interstitial fluid, flavonoids protect $NO^{\cdot}$. Other possible mechanisms of flavonoid vasorelaxation are inhibition of phosphodiesterases (PDE) and lowering Ca^{2+} in smooth muscle cells.

provide advance protection against ischemia–reperfusion injury is not yet investigated.

3. Vasorelaxation

Besides antioxidant effects, flavonoids possess other properties that alleviate ischemia–reperfusion injury; for instance they help to better re-establish blood flow in post-ischemic hearts. A variety of flavonoids and polyphenols have shown the capacity to dilate blood vessels [e.g. 119–123]. Their mechanism of action is various and may be exerted in endothelium-dependent and/or -independent manners. Some polyphenols, such as quercetin and resveratrol, can induce vasorelaxation by both mechanisms [124], although in the absence of endothelium much higher concentrations of polyphenols are probably required [125]. The endothelium-dependent relaxation effect of polyphenols is mediated by nitric oxide.

Nitric oxide ($NO^{\cdot}$) is an important signaling molecule with vasodilatory, anti-inflammatory, and anti-platelet activities [126,127]. The up-regulatory effect of polyphenols on $NO^{\cdot}$ levels occurs through either activation of endothelium nitric oxide synthase (eNOS) or by removing $O_2^{\cdot-}$ and thereby inhibiting consumption of $NO^{\cdot}$ [44,46,128]. Other than increasing eNOS activity [46], flavonoids may additionally induce eNOS expression [129,130]. It has been reported that in ischemic-reperfused hearts a part of beneficial effect of epigallocatechin gallate is mediated through induction of eNOS [25,31]. With resveratrol, Hung et al. [130] reported that intraperitoneal injection of 1 mg/kg 1 h before coronary ligation in rats induced expression of eNOS and nNOS (neuronal NOS) while blocking expression of iNOS (inducible NOS which contrary to eNOS produces excessive amounts of $NO^{\cdot}$ associated with formation of peroxynitrite and oxidative stress). Interestingly, decreases in infarct size and plasma levels of lactate dehydrogenase by resveratrol were $NO^{\cdot}$-dependent, while attenuation of arrhythmia and mortality occurred independently of $NO^{\cdot}$.

As eNOS is a calcium-dependent enzyme, elevation of intracellular Ca^{2+} has been suggested as the mechanism of the endothelium-dependent $NO^{\cdot}$-mediated vasorelaxation by polyphenols [131–134] (Fig. 3). Polyphenols likely increase intracellular Ca^{2+} by stimulating both Ca^{2+} entry from extracellular milieu and Ca^{2+} release from intracellular Ca^{2+} stores [133]. Surprisingly, the rise of Ca^{2+} by polyphenols occurs as a result of increased production of $O_2^{\cdot-}$ as application of superoxide dismutase plus catalase attenuated the Ca^{2+} elevation [135]. These results suggest that the effect of polyphenols on $NO^{\cdot}$ levels can occur both through stimulating $O_2^{\cdot-}$ production inside endothelial cells (stimulating eNOS activity), and through scavenging $O_2^{\cdot-}$ in the interstitial fluid (preserving $NO^{\cdot}$).

$NO^{\cdot}$ is generally produced by eNOS attached to the endothelium plasma membrane [136] and delivered to smooth muscle cells where it manifests its biological functions [137]. In smooth muscle cells, $NO^{\cdot}$ activates guanylate cyclase which synthesizes cyclic GMP (cGMP), an important mediator of vasodilation (Fig. 3). cGMP acts by activating protein kinase G which affects a number of target proteins including those involved in Ca^{2+} channels, decreasing cytosolic Ca^{2+} through activating endoplasmic reticulum Ca^{2+} uptake [138] and inhibiting extracellular Ca^{2+} entry [139]. The eventual low intracellular Ca^{2+} in smooth muscle cells mitigates cellular contractility and yields relaxation. In contrast to the aforementioned polyphenol-induced vasorelaxation, inhibition of $NO^{\cdot}$-cGMP-mediated vasorelaxation has also been observed with some flavonoids [140].

The mechanism of endothelium-independent relaxation by polyphenols is yet uncertain, but signaling pathways downstream of cGMP might be activated in smooth muscle cells independently of $NO^{\cdot}$. Among downstream mechanisms are inhibition of protein kinase C [141] and phosphodiesterases (a family of enzymes responsible for the

breakdown of the vasorelaxants cyclic AMP (cAMP) and cGMP) [142], inhibition of Ca^{2+} influx from extracellular and intracellular resources [143–144], and activation of voltage-gated K^+ channels [145] (Fig. 3). The blockade of extracellular Ca^{2+} influx and endoplasmic reticulum Ca^{2+} release by polyphenols is appealing as it could be one of the possible mechanisms of polyphenol protection of hearts from Ca^{2+} overload in states of ischemia–reperfusion.

Flavonoids may also promote vasorelaxation by stimulating production of prostacyclins by endothelial cells [36,144,146]. In this regard, Maffei Facino et al. [36] found that 3 weeks oral administration of grape seed proanthocyanidins (530 mg/kg diet) increased production of prostacyclins in ischemic and ischemic-reperfused hearts. Proanthocyanidins can also cause vasodilation through suppressing the rennin–angiotensin system by acting as angiotensin receptor antagonist as well as inhibiting angiotensin converting enzyme [147]. Furthermore, vasodilatory effects of flavonoids may partly be exerted by scavenging peroxynitrite and therefore preserving tetrahydrobiopterin from oxidation [52]. Alternatively, resveratrol has shown to elevate tetrahydrobiopterin levels by increasing activity of the rate-limiting enzyme in tetrahydrobiopterin synthesis [148].

A part of the vasodilatory effect of flavonoids may be conferred through inhibiting endothelial NADPH oxidase (as discussed above), which due to production of $O_2^{\cdot-}$ and promoting formation of peroxynitrite likely contributes to endothelium dysfunction [149]. Accordingly, quercetin prevented endothelial dysfunction by inhibiting expression of the $p47^{phox}$ regulatory subunit of NADPH oxidase and thereby decreasing NADPH oxidase-mediated $O_2^{\cdot-}$ production in rat aortic rings pre-contracted with endothelin-1 [141] or angiotensin II [150] and in spontaneously hypertensive rats after 13 weeks oral treatment [120]. Similarly, oral administration of red wine polyphenols for 5 weeks inhibited elevations in aortic NADPH oxidase activity and plasma endothelin-1 levels in experimentally-induced hypertensive rats [151]. Inhibition of NADPH oxidase activity may be one of the underlying mechanisms of flavonoid protection of heart against ischemia–reperfusion injury by the synthetic flavonoid 3′,4′-dihydroxyflavonol [152]. It is noteworthy that the $O_2^{\cdot-}$ scavenging ability of specific flavonoids may differ from their NADPH oxidase inhibitory ability as for example epicatechin scavenged $O_2^{\cdot-}$ but failed to inhibit NADPH oxidase in human umbilical vein endothelial cells [153]. However, methylated forms of epicatechin inhibited NADPH oxidase, while epicatechin glucuronide displayed both properties [153].

4. Anti-inflammatory and anti-aggregatory effects

Cardiac ischemia–reperfusion injury triggers an acute inflammatory response in which neutrophils via chemotactic attraction infiltrate the myocardium and aggravate the situation of the already injured tissue [18]. In their normal path through the systemic circulation when neutrophils arrive to the reperfused tissue, they are exposed to chemotactic agents, mainly released from endothelial cells, and become activated [154]. Endothelial cells, in response to specific stimuli including ROS [155], release chemoattractants such as leukotriene B_4 [156] and adhesion molecules such as intercellular adhesion molecules (ICAM), vascular cell adhesion molecules (VCAM) and selectins, leading to neutrophil attraction, sequestration and adhesion to the microvasculature [155]. Accumulation and sequestration of neutrophils in the coronary microcirculation can lead to the occlusion of the microvasculature and thereby incomplete restoration of blood flow in the reperfused region, causing the “no-reflow” phenomenon [157].

Flavonoids have shown the capacity to inhibit enzymes involved in eicosanoid pathways, including phospholipase A_2, cyclooxygenases and lipoxygenases, thereby limiting production of inflammatory mediators such as prostaglandins and leukotrienes [for reviews see 158–162]. Flavonoids can also inhibit production of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and interferon-γ, as well as chemotactic agents. Inhibitory effects of flavonoids on production of cytokines have not been investigated as a mechanism of flavonoid protection of heart against ischemia–reperfusion injury. However, oral ingestion of red wine, as a source of flavonoids and resveratrol, for 1 year reduced plasma levels of pro-inflammatory cytokines in survivors of a first myocardial infarction [163], although an effect of alcohol was not excluded.

Moreover, flavonoids and other polyphenols have shown inhibitory effects on expression of adhesion molecules such as ICAM-1, VCAM-1, and E-selectin [160,164,165]. For instance, taking 100 mg/day proanthocyanidin supplement for one month decreased plasma concentrations of ICAM-1, VCAM-1, and E-selectin in systemic sclerosis patients [166]. In ischemia–reperfusion studies, perfusing hearts with resveratrol before ischemia decreased the release of adhesion molecules such as ICAM, VCAM, and E-selectins into heart effluents during reperfusion in a $NO^{\cdot}$-dependent manner [167]. Similarly, intravenous administration of genistein 5 min after coronary artery occlusion decreased myeloperoxidase activity and ICAM-1 expression in the ischemic myocardium and decreased levels of TNF-α in serum and macrophages [168].

As a result of the anti-inflammatory function of flavonoids vascular permeability is mitigated and the number of leukocytes adherent to the endothelium is reduced [169,170]. For instance, incubation of TNF-α-induced human umbilical vein endothelial cells with proanthocyanidins decreased expression of VCAM-1, but not ICAM-1, and attenuated leukocyte-endothelial cell interactions [171]. Also, intraperitoneal administration of 7-monohydroxyethylrutoside, a semi-synthetic flavonoid, 1 h before ischemia in mice decreased neutrophil infiltration in post-ischemic myocardium [172]. Similarly, intravenous treatment of rats with epigallocatechin gallate at the end of ischemia and during reperfusion reduced neutrophil infiltration as evidenced by lower myeloperoxidase activity in heart tissues [26].

Consumption of flavonoids for even shorter periods of time may also be beneficial. For instance, one-time consumption of proanthocyanidin-rich chocolate decreased the plasma leukotriene to prostacyclin ratio, an indicator of inflammation, along with an increase in plasma epicatechin [173]. The reduction of leukotrienes likely resulted from inhibition of lipoxygenases [159,174]. Lipoxygenases possess an active ferric form of iron required for their catalytic activity [175]. The activity of lipoxygenases is abolished if the ferric iron is reduced to the ferrous form. ROS can activate the enzyme by oxidizing the ferrous form, while flavonoids are suggested to inactivate it through either scavenging ROS or directly by reducing the ferric form.

The anti-inflammatory effects of flavonoids are mediated to a large extent through blocking activities of the enzymes implicated in signaling pathways especially protein kinase C and mitogen-activated protein kinases (MAPK), with downstream inhibition of transcription factors nuclear factor-kappa B (NF-κB) and activator protein (AP)-1 [158,160,161,164]. For instance, in ischemic-reperfused hearts, intravenous administration of epigallocatechin gallate decreased plasma levels of IL-6 and inhibited NF-κB and AP-1 activation [26]. Elevation of cAMP secondary to inhibition of phosphodiesterases has also been suggested as a mechanism for the anti-inflammatory activity of flavonoids [160]. Flavonoid inhibition of protein kinases has been suggested to occur through competitive binding of flavonoids with ATP at the active site of the enzymes.

As with other properties, anti-inflammatory effects of flavonoids depend on the type of the flavonoid and therefore differ from one flavonoid to another. These effects may vary even when flavonoids are from the same category. For instance, small molecules of proanthocyanidins (e.g. dimers and trimers) suppressed, while comparably larger molecules (e.g. pentamers) stimulated expression of IL-1β [159]. For vasodilation, an effect contrary to this was observed; whereas big polymers of proanthocyanidins showed endothelium-dependent relaxation on rabbit aortic rings, small molecular weight proanthocyanidins failed to exhibit such an effect.

Flavonoids have also shown to inhibit platelet activation and aggregation [147,176], an event which occurs following heat ischemia–reperfusion [177]. The anti-platelet effect of flavonoids may be due to increased production of prostacyclin [36] which via synthesis of cAMP reduce platelet aggregation [178]. Accordingly, de-alcoholized red wine and its catechin-anthocyanidin fraction exhibited anti-platelet aggregatory activity associated with increased cAMP [179]. Flavonoids may also decrease platelet activation through inhibition of phosphodiesterases responsible for degradation of cAMP [160]. Furthermore, given that $NO^{\cdot}$ has a protective role in maintaining non-adhesive endothelium [180] and considering that flavonoids are stimulators of $NO^{\cdot}$ generation, they may inhibit adhesion of leukocytes and platelets to the endothelium through up-regulation of $NO^{\cdot}$ [47]. Freedman et al. [47] reported that in healthy individuals who ingested purple grape juice for 14 days inhibition of platelet aggregation was accompanied with enhanced platelet-derived $NO^{\cdot}$ production. Moreover, as inflammatory responses are greatly induced by oxidative stress, flavonoid inhibition of inflammation and platelet aggregation may be at least partly due to attenuation of oxidative stress. Recently, a flavonoid extract was shown to protect from myocardial reperfusion injury, purportedly by blocking the action of platelet activating factor [181].

5. Inhibition of metalloproteinases

Matrix metalloproteinases (MMP) are a family of proteases that play a major role in protein degradation and tissue remodeling [182]. Elevation of plasma levels of MMP has been documented after ischemia–reperfusion-related morbidities such as myocardial infarction [183], restenosis [184], and heart failure [185]. Since increased activity of MMP is associated with ventricular dilation and cardiac remodeling [186], inhibitors of MMP may play as effective strategies to prevent chronic consequences of the injury [187,188].

Polyphenolic compounds in red wine and green tea have shown ability to inhibit activation of metalloproteinase-2 [189]. In green tea, the inhibitory effect seemed to correlate with the gallic acid moiety of the catechins as the inhibitory activity of epigallocatechin gallate and epicatechin gallate was more than that of epigallocatechin while catechin and epicatechin showed the least effect [190]. Epigallocatechin gallate dose-dependently decreased activation of metalloproteinase-2 in human umbilical endothelial cells [191]. Similarly, quercetin dose-dependently decreased expression of metalloproteinase-9 in human aortic smooth muscle cells [192]. The flavonoid inhibition of metalloproteinases has also been demonstrated in ischemic-reperfused hearts. Yamazaki et al. [28] reported that 10 days oral pre-treatment of rats with 1 mg/kg/day epicatechin prevented an increase in metalloproteinase-9 in the infarct zone 48 h after 45 min coronary occlusion. The inhibition of metalloproteinases by phenolic compounds has been speculated to occur transcriptionally through suppression of DNA binding activity of NF-κB and AP-1 [193,194]. Moreover, quercetin has shown to stimulate expression of metalloproteinase-1 tissue inhibitor in human vascular endothelial cells treated with oxidized LDL [195]. It has been suggested that high doses of polyphenols inhibit activation of metalloproteinases and prevent angiogenesis, while low doses of polyphenols show angiogenic effects without altering activity of metalloproteinases [196].

6. Conclusions

Despite that flavonoids are well-known as antioxidants emerging evidence demonstrates that mechanisms behind their effects are more extensive than previously thought. They exert many of their effects through interaction with cellular signaling pathways. Signaling pathways are mostly regulated by oxidation-reduction changes in the redox-sensitive sites of critical structural and biological proteins, giving plenty of opportunity for flavonoids and other antioxidants to modify these pathways. Myocardial ischemia–reperfusion causes a wide range of complications largely as a result of oxidative stress-induced alterations in signal transduction pathways. The interactions of flavonoids with such pathways have begun to be recognized in more detail. A greater understanding of the ways by which different flavonoids may protect the heart from ischemia–reperfusion injury can be used to establish effective therapeutic interventions with isolated flavonoids or flavonoid-rich foods.

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