Polyphenols: potential source of drugs for the treatment of ischaemic heart disease

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Abstract

Polyphenols, which are naturally present in plants, have been studied for their chemical and pharmacological properties. Polyphenols have been found to exhibit various bioactivities such as antioxidant, free radical scavenging and anti-inflammatory effects, in addition to regulating the intracellular free calcium levels. These bioactivities are related to the underlying mechanisms of ischaemic heart diseases. Pharmacological studies have proven polyphenols to be effective in treating cardiovascular diseases in various ways, particularly ischaemic heart diseases. Based on their mode of action, we propose that some polyphenols can be developed as drugs to treat ischaemic heart diseases. For this purpose, a strategy to evaluate the therapeutic value of drugs for ischaemic heart diseases is needed. Despite several advances in percutaneous coronary intervention (PCI), the incidence of myocardial infarction and deaths due to cardiovascular diseases has not decreased markedly in China. Due to their pleiotropic properties and structural diversity, polyphenols have been of great interest in pharmacology. In the present review, we summarize the

pharmacological effects and mechanisms of polyphenols reported after 2000, and we analyse the benefits or druggability of these compounds for ischaemic heart diseases.

Abbreviations

ACEI: angiotensin-converting enzyme inhibitor;
ADMA: asymmetric dimethylarginine;
ADP: adenosine diphosphate;
ADR: adenosine receptor;
AMPK: adenosine monophosphate-activated protein kinase;
CAD: coronary artery disease;
cGMP: cyclic guanosine monophosphate;
COPD: chronic obstructive pulmonary disease;
COX: cyclooxygenase;
EC: endothelial cell;
EGCG: epigallocatechin gallate;
ER: oestrogen receptor;
FAO: fatty acid oxidation;
GPx1: glutathione peroxidase 1;
HUVECs: human umbilical vein endothelial cells;
IHD: ischaemic heart disease;
LPO: lipid peroxidation;
NADPH: nicotinamide adenine dinucleotide phosphate;
NF- κ B: nuclear factor kappa B;
NO: nitric oxide; PDEs: phosphodiesterases;
OPR: opioid receptor;
PA: protocatechuic acid;
PCI: percutaneous coronary intervention;
PGI₂: prostacyclin I₂;
PI3K: phosphoinositide 3-kinase;
PKA: protein kinase A;
SalA: salvianolic acid A;
SalB: salvianolic acid B;
SIRT1: deacetylase sirtuin 1;
SOD: superoxide dismutase;
SP-1: specificity protein-1;
TXA₂: thromboxane A₂;

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1. Introduction

Ischaemic heart disease (IHD) is considered the leading cause of death and disability worldwide. It is characterized by insufficient blood supply to the heart due to the pathological narrowing of coronary vessels, typical of atherosclerosis. The clinical characteristics of IHD include temporary pain (angina), irregular heartbeat (arrhythmia), permanent heart muscle damage (myocardial infarction) and loss of muscle activity (heart failure).

IHD is managed with medication and surgery. The following drugs are used to manage IHD: 1) nitroglycerine, which decreases oxygen demand and increases oxygen supply by causing the coronary artery to dilate; 2) statins, which reduce cholesterol level, improve vascular endothelial function, dilate blood vessels and inhibit inflammatory reaction; 3) angiotensin-converting enzyme (ACE) inhibitors, which reduce angiotensin II production by inhibiting ACE, increase myocardial blood flow, reduce myocardial oxygen consumption, inhibit inflammatory responses and may lower the risk of recurrent myocardial infarction; 4) calcium channel blockers, which exert cardioprotective effects by lowering the intracellular calcium level, relaxing vascular smooth muscle and dilating the blood vessels; 5) β -receptor antagonists, which reduce myocardial oxygen consumption by suppressing the effects of adrenaline; 6) anti-platelet agents, such as aspirin and clopidogrel, to inhibit platelet aggregation and lower the risk of atheromatous plaque formation; and 7) cell- and protein-based therapies, which help restore organ function and myocardial regeneration.

At present, percutaneous coronary intervention (PCI) with drug-eluting stents (DESs) is used to reduce cardiovascular events in patients with coronary artery disease (CAD) and IHD. Although it significantly reduced restenosis rates, the use of DES increased the risk of both late stent thrombosis and atherosclerosis, and in turn late stent failure. Many patients, especially the elderly, are deemed unsuitable for revascularization due to co-morbid diseases, unsuited anatomy or the risks inherent to the procedure (Bonetti, Holmes, Lerman, & Barsness, 2003). Moreover, despite several advances in PCI, the incidence of myocardial infarction and deaths due to cardiovascular disease has not decreased visibly in China (Sui, Chen, & Wang, 2015). Therefore, pharmacological interventions for IHD have been of great interest recently.

Polyphenols constitute a large group of natural products widely distributed

across the plant kingdom. Based on the number of phenol rings and the binding structural properties, polyphenols are divided into several subclasses such as phenolic acids, flavonoids, stilbenes, lignans and tannins. In the past decades, several different polyphenols have been isolated and identified from plants, in addition to their pharmacological activities (Goszcz, et al., 2015). The evidence points to the multiple pharmacological effects of polyphenols against cardiovascular diseases, particularly IHD. For IHD, the underlying mechanisms of action of polyphenols have been elucidated. These include reducing myocardial oxygen consumption and/or increasing oxygen supply, enhancing myocardium metabolism after ischaemia/reperfusion (I/R), inhibiting platelet aggregation and thrombosis, regulating lipid metabolism and inflammation to inhibit the formation of atheromatous plaques, promoting angiogenesis or endothelial cell (EC) repair, protecting the remaining myocardial cells and restoring myocardial contraction (Harasym & Oledzki, 2014; Raj, Zieroth, & Netticadan, 2015).

For this review, we systematically searched the EMBASE, PubMed and Cochrane Library databases, and the references of relevant papers. Combined with the results obtained in our laboratory, we presented an overview of the advances in elucidating the effects of polyphenols (including their derivatives and analogues) against IHD. In the following sections, we classify their pharmacological activity and functional mechanisms, particularly those with therapeutic potential for IHD.

2. Polyphenols

2.1 Flavonoids

Flavonoids are an important class of polyphenols abundantly found in vegetables, fruits and different plants; they are usually yellow in colour. Approximately 2% of the total carbon in a plant is ultimately converted to flavonoids or similar compounds. Chrysin (Figure 1A) was the first flavonoid to be isolated (1814). To date, >4000 flavonoids have been isolated and identified (Iwashina, 2000). Flavonoids such as quercetin (Figure 1B), rutin (Figure 1C) and hesperidin (Figure 1D), isolated from fruits, are most commonly studied for their cardiovascular effects. Furthermore, anthocyanins are common dietary flavonoids that help prevent cardiovascular disease. Although many flavonoids have been isolated, several more flavonoids are yet to be discovered.

The basic skeleton of flavonoids is composed of C₆–C₃–C₆, generally containing

two aromatic rings, a central three-carbon chain and a 4-carbonyl group. Flavonoids are widely used as antioxidants as they possess several phenolic hydroxyl groups that donate active hydrogen atoms and stop/delay the automatic oxidation of lipids. Many flavonoids have been found to exhibit various pharmacological actions except antioxidation. For example, pinocembrin (Figure 1E), isolated from honey and propolis, is an anti-inflammatory and antimicrobial agent that acts on diastolic arteries (Estevinho, et al. 2008; Li, et al., 2013; Rasul, et al., 2013). Baicalein (Figure 1F), isolated from the roots of the labiate *Scutellaria baicalensis*, can scavenge oxygen-derived free radicals and protect the heart, cerebral vessels and neurons (Xin, et al., 2014). It is worth noting that Veregen contains a mixture of known active compounds, including catechins (Figure 1K). On 31 October 2006, the Food and Drug Administration (FDA) approved the use of Veregen for treating perianal and genital condyloma (Hara, 2011).

Figure 1. The chemical structures, molecular formulas and molecular weights of selected flavonoids. These flavonoids were selected because they were most commonly studied with significant cardiovascular effects. A: chrysin; B: quercetin; C: rutin; D: hesperidin; E: pinocembrin; F: baicalein; G: 3'-O-methyl-quercetin; H: quercetin-3-O-glucuronide; I: genistein; J: daidzein; and K: catechin.

2.2 Phenolic acids

Phenolic acids constitute another important class of polyphenols found in plants with well-established bioactivities. Both *in vivo* and *in vitro*, most of the phenolic acids showed antioxidative, anti-inflammatory and free radical scavenging activities, and could protect cells against injuries induced by various harmful factors.

Phenolic acids with varying chemical structures show different bioactivities. For example, phenolic acids isolated from a variety of legumes showed significant differences in phytochemical content and functional activities (Yao, et al. 2011). Protocatechuic acid (PA) is a naturally occurring phenolic acid found abundantly in >500 plants. It is structurally similar to other well-known antioxidants such as gallic acid, caffeic acid and vanillic acid. It exhibits different pharmacological effects such as its antioxidant activities, anti-inflammatory properties and interaction with several enzymes (Kakkar. & Bais. 2014). Ferulic acid is a simple phenolic acid found in cereals. Spontaneously hypertensive rats (SHRs) treated with ferulic acid (50 mg·kg⁻¹·d⁻¹) showed reduced systolic blood pressure, left ventricular diastolic stiffness, attenuated inflammatory cell infiltration, etc. (Alam, Sernia, & Brown. 2013). In rats fed an atherogenic diet, veratric acid was found to significantly attenuate systolic and diastolic blood pressure and lipid peroxidation products after oral administration (40 mg/kg) for 30 days. In particular, it showed protective effects against atherogenic diet-induced hyperlipidaemia (Raja, Saravanakumar, & Sathya, 2012). Salvianolic acids have been isolated from *Salvia miltiorrhiza* for use against cardiovascular diseases in traditional Chinese medicine for thousands of years (also known as *Danshen*) (Li, et al., 2007). To date, >10 different salvianolic acids have been identified: salvianolic acid A, B, C, D, E, F, G, etc. (Figure 2). Compared with the flavonoids in *Danshen*, salvianolic acids exhibit more potent antioxidant activity, among other bioactivities. Although these compounds directly scavenge free radicals, they may not be present at the high concentrations required *in vivo*. Their antioxidant activity may lead to the inhibition

of pro-oxidant enzymes and the up-regulation of the expression of antioxidant enzymes, such as the activation of the Nrf2/haeme oxygenase-1 (HO-1) pathway (Pignatelli, et al., 2006; Zhang, et al., 2014). It is worth noting that polyphenols can also induce pro-oxidant responses in ECs leading to endothelial NO synthase activation as well as in cancer cells leading to apoptosis (Wang, et al., 2013). However, the pro-oxidant responses were concentration related. In addition, they showed tissue and cell specificity. This indicates that pro-oxidant responses can only be induced at a particular concentration in tissues and cells, which is very rare.

In general, the chemical structures of salvianolic acids possess the danshensu ((3, 4-dihydroxyphenyl) lactic acid) unit, a simple monomeric compound isolated from *Danshen*. More precisely, these compounds are typically depsides of danshensu and caffeic acid derivatives with phenolic hydroxyl groups.

Figure 2. Chemical structures of phenolic acids and polyphenols. A: salvianolic acid A; B: salvianolic acid B; C: salvianolic acid C; D: salvianolic acid D; and E: resveratrol.

2.3 Others

Various other polyphenol compounds, such as stilbenes, lignans and tannins, have been identified and studied for their therapeutic potential. These polyphenols have been found to have multiple cardiovascular effects. For example, resveratrol (Figure 2E) exhibits antioxidant and anti-inflammatory activities, prevent cell damage induced by oxidative stress, hypoxia and ischaemia (Carrizzo, et al., 2013; J. Li, et al., 2015; Lu, et al., 2010).

3. Cardiovascular activities of polyphenols

3.1 Decrease in heart oxygen consumption or increase in oxygen supply

The induction of coronary artery dilation is considered an important therapeutic strategy for IHD, as it restores the blood supply to the ischaemic area and minimizes the related damage.

Many studies have implicated nitric oxide (NO) in the modulation of I/R injury (Bice, Jones, Chamberlain, & Baxter, 2016). As a critical regulator of vascular tone, NO acts as a vasodilator by activating soluble guanylyl cyclase, subsequently increasing cyclic guanosine monophosphate (cGMP) in vascular smooth muscle cells. cGMP can be metabolized by cyclic nucleotide phosphodiesterases (PDEs). When the production and bioavailability of NO are adequate, vascular homeostasis is achieved. In myocardial ischaemia, the oxygen supply/demand ratio decreases while free oxygen radicals accumulate, thus reducing the bioavailability of NO. Because the O_2^- radical is implicated in the destruction of NO, it is important to establish whether NO may be made more bioavailable with increased antioxidant effects such as neutralizing the O_2^- radical and reducing its concentration. Hence, reduced levels of NO-destroying oxygen radicals can help in the dilation of coronary arteries.

Polyphenols extracted from grapes and wine (e.g., quercetin, tannic acid, resveratrol and malvidin) were found to increase coronary flow via endothelium-dependent relaxations (Fitzpatrick, Hirschfield, & Coffey, 1993). Subsequent studies have shown that polyphenols lower the levels of NO-destroying oxygen radicals by scavenging these free radicals. In addition, polyphenols have been shown to promote NO production in ECs directly by inducing the overexpression of the endothelial nitric oxide synthase (eNOS) or by increasing eNOS activity. The

pharmacological effects of polyphenols on myocardial ischaemia by either a decrease in oxygen demand or an increase in oxygen supply are summarized in Table 1. Polyphenols have also been found to scavenge free oxygen radicals and reduce oxidative stress by modulating glutathione (GSH) concentration, malondialdehyde (MDA) generation and the activities of pro-oxidant and antioxidant enzymes.

Salvianolic acid B (SalB) elevated the plasma NO levels via the nitrate reductase process, as observed in a rabbit heart I/R model, performed half an hour after ligation of the left anterior descending coronary artery (LADCA) and 1–4 hours for reperfusion (Yang, et al., 2008). In subsequent studies, SalB (40 mg/kg) was found to attenuate myocardial ischaemia injury in C₅₇ mice and eNOS^{-/-} mice by producing NO via eNOS phosphorylation, L-arginine uptake and cationic amino acid transporters expression (Pan, et al., 2011).

Resveratrol (3,5,4'-trihydroxy-trans-stilbene, Figure 2E), a plant-derived phenolic acid compound, increases the bioavailable NO content in SHR by preventing NO and eNOS uncoupling. Resveratrol has been found to up-regulate eNOS activity by the following mechanisms: 1) The eNOS messenger RNA (mRNA) level is increased and mRNA stabilized in ECs (Wallerath, et al., 2002). 2) The eNOS phosphorylation ratio at the serine 1177 residue is increased to enhance eNOS activity by intensifying the interaction between oestrogen receptor α (ER α) and Src-caveolin-1 at a concentration of 50 nM, which can be easily reached in vivo (Klinge, Wickramasinghe, Ivanova, & Dougherty, 2008). 3) The intracellular levels of the endogenous eNOS inhibitor asymmetric dimethylarginine (ADMA) are decreased at concentrations ranging from 0.1 to 10 μ M (Frombaum, et al., 2011). 4) The eNOS activity is enhanced by inducing the SIRT1-mediated deacetylation of lysines 496 and 506 in the calmodulin-binding domain of eNOS (Mattagajasingh, et al., 2007).

Frombaum et al. indicated that piceatannol (4-[(E)-2-(3,5-dihydroxyphenyl)ethenyl] benzene-1,2-diol), as a resveratrol analogue, is more effective than resveratrol in restoring the expression and activity of the eNOS regulator dimethylarginine dimethylaminohydrolase in ECs under high-glucose oxidative stress.

Hydrolysable tannins, another group of phenolic acids isolated from the leaves of *Rhus coriaria*, show anti-ischaemic activity and endothelium-dependent vasorelaxant effects in isolated rabbit hearts and thoracic aortae at concentrations of 150–500

µg/mL; the mechanisms included cyclooxygenase (COX) pathway activation, tumour necrosis factor alpha (TNF-α) inhibition, eNOS activation and free radical and reactive oxygen species (ROS) scavenging (Beretta, Rossoni, Santagati, & Facino, 2009).

Some flavonoids have been shown to induce endothelium-dependent vasodilation by increasing the bioavailability of NO. The flavonoid quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one) (Figure 1B) is most naturally prevalent, with reported endothelium-dependent vasodilatory effects via an increase in the bioavailability of NO. Perez-Vizcaino and Duarte reviewed the mechanisms of quercetin-induced NO production. Firstly, under conditions of enzymatically or chemically increased O_2^- and thus accelerated NO metabolism, biomolecules such as quercetin, genistein, daidzein, biochanin A and ginkgo flavone aglycone will directly scavenge free oxygen radicals and therefore protect NO in cell-free systems or in ECs (López-López, et al., 2004). Secondly, flavonoids such as quercetin and monoacetyl-vitexin rhamnoside inhibit enzymatic sources of oxygen, such as xanthine oxidase and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Busse, Kopp, & Middleton, 1984). Thirdly, quercetin prevents BH4 oxidation and eNOS uncoupling (Romero, et al., 2009). Fourthly, under normal conditions, quercetin stimulates eNOS activity in a dose- and time-dependent manner following a sudden increase in intracellular Ca^{2+} concentrations, with a concomitant increase in NO production in ECs (Kuhlmann, et al., 2005). It is worth noting that quercetin is extensively metabolized into methylated and glucurono- and sulpho-conjugated forms that circulate in the plasma. Further, the glucurono-conjugates can be hydrolysed to the parent aglycone, which in turn accumulates in tissues and exerts vasodilatory and antihypertensive effects (Duarte & Pérez-Vizcaino, 2015).

Like resveratrol, most flavonoids up-regulate eNOS expression at both the mRNA and protein levels. This effect is mediated at least in part by SIRT1 and by hyperpolarization-dependent Ca^{2+} entry. Dimethylarginine dimethylaminohydrolase can regulate NO synthesis (Frombaum, et al., 2011; MacAllister, et al., 1996). In addition to NO, endothelium-dependent hyperpolarization can also lead to endothelium-dependent vasodilation. Quercetin is known to induce hyperpolarization-mediated endothelium-dependent relaxation and vasodilatation

(Kuhlmann, et al., 2005). Furthermore, some flavonoids are potent inhibitors of PDE, which may contribute to their vasodilatory responses (Peluso, 2006; Ruckstuhl, Beretz, Anton, & Landry, 1979).

Studies of human umbilical vein endothelial cells (HUVECs) have shown that 10 μ M quercetin aglycone minimally reduces the eNOS level and significantly reduces the expression of ET-1, whereas human metabolites had no effect (Tribolo, et al., 2013). In human aortic ECs, 5 and 10 μ M quercetin and its metabolites (3'-O-methyl-quercetin and quercetin-3-O- glucuronide; Figure 1G, H) showed protective effects by activating adenosine monophosphate-activated protein kinase (AMPK) and inducing eNOS activity. These compounds caused an increase in S-nitrosothiol and nitrite concentrations (Shen, et al., 2012). Pretreatment of arteries with 5 and 10 μ M quercetin or its metabolites was found to prevent endothelium dysfunction in isolated C57BL mouse aortic rings (Shen, et al., 2012).

Catechin, a flavan-3-ol, is a naturally occurring flavonoid with antioxidant properties. Epigallocatechin gallate ((2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3-yl 3,4,5-trihydroxybenzoate, EGCG; Figure 1K) is a potent antioxidant and the most abundant catechin (water-soluble polyphenol) in tea. EGCG can modulate ROS production and eNOS activation, increase endothelium-derived NO levels via a PI3-kinase-dependent pathway in SHR and enhance coronary flow (Potenza, et al., 2007). In rat aortic rings, EGCG has also been shown to cause endothelium-dependent vasodilation at concentrations of 1–50 μ M by activating eNOS via phosphatidylinositol 3-kinase-, protein kinase A (PKA)- and Akt-dependent pathways (Lorenz, et al., 2004). EGCG is also known to preserve the bioavailability of NO by reducing the levels of the endogenous NOS inhibitor ADMA (Tang, Hu, et al, 2006). Recent findings indicate that these effects are typical of the metabolites of EGCG. EGCG metabolites produced by intestinal bacteria also inhibit ACE (Takagaki & Nanjo, 2015).

Some flavonoids have been shown to cause endothelium-dependent vasodilation that is highly dependent on PDE activity. Monoacetyl-vitexin rhamnoside, a flavonoid extracted from *Crataegus* species known to inhibit PDE, was suggested to improve myocardial perfusion in several isolated heart models (Schussler, Holzl, Rump, &

Fricke, 1995). API0134 from *Andrographis paniculata* improved cardiac function in dogs, decreased the extent of myocardial infarct size, alleviated the extent of myocardial injury and decreased the incidence of arrhythmias (Guo, Zhao, & Fu, 1996). API0134 was also found to promote the production of prostaglandin, increase the prostacyclin I2 (PGI2) to thromboxane A2 (TXA2) ratio and inhibit the production of free radicals from granulocytes. API0134 also scavenges H_2O_2 , O_2^- and OH significantly and inhibits the induced aggregation of washed human platelets. In addition, it significantly increases the NO and cGMP content and superoxide dismutase (SOD) activity, decreases endothelin and lipid hydroperoxide contents and maintains the NO/endothelin balance (Wang, Zhao, & Xiang, 1997).

Phyto-oestrogens have been associated with decreased aortic stiffness, as measured by aortic pulse-wave velocity (Van der Schouw *et al.*, 2002). Phyto-oestrogens such as genistein (Figure 1I) and daidzein (Figure 1, J) have been shown to relax pre-contracted coronary artery rings and mesenteric arterial rings of rabbit in a concentration-dependent manner. Like oestrogens, phyto-oestrogens relax arteries by significantly restoring the NO levels (Figtree, *et al.*, 2000).

3.2 Anti-atherosclerotic and cardioprotective activities

Myocardial infarction therapy is more effective when atherosclerotic plaque formation is inhibited and the risk of thrombosis reduced. Restoration of endothelial function is an important approach, as the functional endothelium plays a critical role in anti-atherosclerotic and anti-thrombotic action. The cardiac endothelium is composed of endocardial ECs lining the heart chambers and vascular ECs lining the coronary microvasculature. Vascular EC-derived NO is a significant endogenous anti-atherosclerotic and anti-thrombotic molecule. It is known to inhibit the proliferation and migration of smooth muscle cells; enhance EC proliferation and migration; inhibit apoptosis; suppress platelet aggregation; and preventing platelet, leucocyte and monocyte adhesion to the endothelium. However, in myocardial ischaemia, the decrease in the oxygen supply/demand ratio leads to the accumulation of free oxygen radicals, which increases the risk of atherosclerotic plaque formation and thrombosis. As antioxidants, polyphenols enhance the bioavailability of NO or

assist in the delivery of NO. Other anti-atherosclerotic and anti-thrombotic effects on blood cells and the vascular wall have also been studied.

Another study showed that the vasorelaxation effect reduced the incidence of coronary heart disease, the effect being mediated by the NO–cGMP pathway in some polyphenols (Fitzpatrick, et al; 1993). A recent study reported that anthocyanin supplementation could improve endothelium-dependent vasodilation by activating the NO–cGMP signalling pathway, enhancing the serum lipid profile and inhibiting inflammation (Zhu, Y, et al., 2011).

Resveratrol is widely used, as it prevents atherosclerosis via NO-dependent and NO-independent mechanisms. The NO-dependent mechanism of resveratrol is summarized as follows: First, resveratrol prevents superoxide production from NADPH oxidase and from the mitochondria. Second, resveratrol enhances the expression of several antioxidant enzymes including SOD isoforms, glutathione peroxidase 1 (GPx1), CAT and HO-1 (Li, Xia, & Forstermann; 2012). Moreover, resveratrol is known to reverse eNOS uncoupling in hypercholesterolaemic ApoE-knockout (KO) mice by preventing BH₄ oxidation and stimulating BH₄ biosynthesis via upregulation of guanosine triphosphate (GTP) cyclohydrolase I (GTPCH1). Furthermore, resveratrol is also known to stimulate NO production by enhancing eNOS expression and activity via multiple mechanisms, including ER-mediated eNOS serine 1177 phosphorylation and SIRT1-mediated eNOS deacetylation. Polyphenols with similar structure to resveratrol are more likely to induce NO formation.

Resveratrol has also been proven to show anti-atherosclerotic and anti-thrombotic effects in a NO-independent manner by suppressing platelet adhesion, activation and aggregation, and in turn preventing thrombogenesis. Furthermore, resveratrol was shown to be a potent inhibitor of both nuclear factor kappa B (NF- κ B) activation and NF- κ B-dependent gene expression by inhibiting inhibitor of kappa B (I κ B) kinase activity (Holmes-McNary & Baldwin; 2000). Moreover, *in silico* docking results suggested that resveratrol forms stable complexes with platelet COX-1. Subsequent *in vitro* studies confirmed that resveratrol inhibits COX-1; modifies COX metabolite production to regulate platelet activation; and blocks the

arachidonate-dependent synthesis of inflammatory agents such as thromboxane B₂, hydroxyheptadecatrienoate and 12-hydroxyeicosatetraenoate (Crescente, et al., 2009).

Salvianolic acid A (SalA, Figure 1D) (2.5–10 mg/kg, *i.v.*) has been shown to significantly reduce thrombus weight in a murine model of an arteriovenous shunt. The anti-thrombotic effect may be related to its anti-platelet action and modulatory effect on haemorheology without affecting the coagulation system (Fan, et al., 2010). The anti-platelet and anti-thrombotic activities of SalA can be attributed to the inhibition of phosphoinositide 3-kinase (Huang, et al., 2010). Recently, SalA was shown to attenuate hypoxia-induced endothelial endoplasmic reticulum stress and apoptosis via down-regulation of very low-density lipoprotein (VLDL) receptor expression (Xie, Duan, Guo, Hu, & Yu, 2015). It was also found to inhibit platelet-derived growth factor (PDGF)-BB-induced proliferation and migration of vascular smooth muscle cells, thus indicating the anti-atherogenic effects of SalA (Sun, et al., 2012).

SalB has been shown to exhibit anti-atherogenic effects in various studies. SalB prevented the oxidation of low-density lipoprotein (LDL) and inhibited lipid peroxidation by antagonizing the binding of oxLDL to CD36, in turn preventing the formation of foam cells (Karmin, et al., 2001). It also attenuated multiple inflammatory factors and inhibited the associated pathways including the expression of COX-2 (Chen, et al., 2006), matrix metalloproteinase (MMP)-2 and MMP-9 (Lin, et al., 2007) and TGF- β /Smad (Wang, Tao, Yuan, Shen, & Liu, 2010) or NF- κ B signalling pathways (Wang, Hu, Gao, Guo, & Fan, 2010), which may be involved in CD36-related pathways, thus leading to atherosclerotic and other vascular diseases. SalB (50 and 100 μ M) inhibited PDGF-induced cell proliferation and migration, and markedly increased HO-1 expression via the reduction of reactive oxygen species and the NADP/NADPH ratio in vascular smooth muscle cells (Lee, MiRanSeo, & Lee, 2014). In addition, SalB directly inhibited platelets isolated from Sprague-Dawley (SD) rat plasma in a dose-dependent manner (Li, et al., 2004). Wu et al. found that SalB inhibited platelet deposition, in a dose-dependent manner, from flowing, anti-coagulated whole blood to immobilized collagen at both venous and arterial shear rates by interfering with the collagen receptor α 2 β 1 (Wu, et al., 2008). In a recent study, Xu et al. showed that SalB attenuated platelet-mediated inflammatory responses by inhibiting NF- κ B activation in ECs even if the platelets were activated

previously (Xu, et al., 2015).

Several molecular mechanisms have been proposed for the anti-platelet aggregation action of flavonoids: oxidative stress, protein tyrosine phosphorylation, calcium mobilization and NO pathway (Haouari & Rosado, 2011). Gryglewski et al. were the first to attribute the anti-thrombotic effects of flavonols to their ability to scavenge superoxide (Gryglewski, 1987). They also attributed these effects to the inhibition of cyclic nucleotide PDEs and a subsequent increase in cAMP levels. Subsequently, the inhibitory effects of quercetin on protein kinase C (PKC)-dependent NADPH oxidase activation in platelets were established (Pignatelli, et al., 2006). In a recent study, reduced Fyn kinase activity as well as Syk and phospholipase C activation was implicated in the anti-aggregation effects of quercetin (Wright, et al., 2010). These effects were examined in vivo as well; however, Janssen et al. found no change in platelet aggregation, thromboxane B2 production, factor VII levels or other metrics when evaluating blood samples from 114 healthy volunteers receiving a dietary quercetin supplement (Janssen, et al., 1998).

Cocoa procyanidins stimulate the formation of a platelet aggregation inhibitor PGI₂. These compounds also inhibit the formation of leukotrienes, which act as vasoconstrictors and stimulate inflammation (Manna, Mukhopadhyay, & Aggarwal, 2000). Therefore, cocoa polyphenols inhibit coagulation and promote blood flow, thus preventing thrombosis (Csiszar, et al., 2008).

3.3 Protective effect on myocardial cells and cardiac remodelling

Ischaemia and I/R can sometimes lead to cell death. It is worth noting that a delay in reperfusion can exacerbate ischaemic damage, as more ROS are produced when blood flow to the occluded artery is resumed. Thus, in principle, protecting cardiomyocytes from I/R-induced cell death would increase the viability of the myocardium, which is beneficial in both the short and long term after myocardial infarction. Therefore, cardiomyocyte apoptosis represents an excellent target in the treatment of myocardial infarction and I/R injury.

In recent studies, novel mechanisms of the myocardial protective action of polyphenols have been proposed: protection of mitochondrial function and the regulation of epigenetic modification-related enzyme activity. Moreover, polyphenols can also improve cardiac hypertrophy, ventricular remodelling and fibrosis after MI

(Jiang, Chang, & Dusting, 2010). In particular, polyphenols inhibiting cardiac remodelling or preventing myocardial apoptosis are summarized in Table 3.

In the 1990s, pharmacologists reported that SalA could protect the heart from I/R-induced damage both in vivo and in vitro (Du, Qiu, & Zhang, 1995). Further research shows that SalA protects not only the heart in different animal models but also the vascular functions in normal and diabetic animal models when administrated orally or injected intravenously. SIRT1, a histone acetyltransferase, has been implicated in the regulation of hypoxia-induced and I/R-induced apoptosis in cardiomyocytes. Resveratrol has been proven to protect cells from apoptosis at low concentration by activating SIRT1. For example, in the cardiomyoblast cell line H9C2, 20 μ M resveratrol causes the rapid activation of SIRT1 and stimulates FoxO1 to induce cell cycle arrest, although it inhibits FoxO1-induced cell death. This indicates that resveratrol inhibits hypoxia-induced apoptosis in rat cardiac myoblasts (H9C2 cells) via the SIRT1–FoxO1 pathway (Chen, et al., 2009). Recently, resveratrol has been shown to up-regulate the expression of SIRT1 and to alleviate cardiac oxidative damage and left ventricular remodelling in an aged emphysema rat model. This indicates the therapeutic potential of resveratrol for cardiac injuries complicated by chronic obstructive pulmonary disease (COPD) (Hu, et al., 2013). More recently, resveratrol has been shown to reduce the ageing effect and alleviate hypoxia–reperfusion (H/R) injury in cardiomyocytes during hypoxic preconditioning (HPC) depending on the regulation of SIRT1 (Zheng, Guo, Hong, Zheng, & Wang, 2015). In addition, as an activator of SIRT1, resveratrol extends the lifespan of *Caenorhabditis elegans* (Morselli, et al., 2010) and protects the rat myocardium from I/R injury (Lekli, et al., 2010) via autophagy, as sirtuins have been proven to stimulate autophagy by deacetylation of autophagic proteins.

Mitochondrial, biochemical and morphological changes are typically observed in ischaemic cardiomyocytes, and these are also considered to be another cause of I/R cardiomyocyte apoptosis. Resveratrol has gained interest in regulating mitochondrial dysfunction due to its effects on mitochondrial oxidative stress. In pigs with metabolic syndrome fed a high-cholesterol diet, resveratrol treatment lead to increased phosphorylation of mammalian target of rapamycin (p-mTOR) and decreased levels of p70 S6 kinase (P70S6K), lysosome-associated membrane protein (LAMP)-2 and autophagy-related gene 12-5 conjugates. These results suggested that resveratrol

regulates autophagy signalling in chronic myocardial ischaemia (Sabe, Elmadhun, Dalal, Robich, & Sellke, 2014).

Polyphenols also function via specific signalling pathways to reduce I/R-induced cardiomyocyte apoptosis. For example, resveratrol protects cardiomyocytes against anoxia/reoxygenation injury via the Toll-like receptor 4 (TLR4)/NF- κ B signalling pathway. This indicates that the anti-apoptotic effect of resveratrol is associated with its anti-inflammatory effect (Zhang, et al., 2012). In addition, resveratrol exerts cardioprotective effects by activating adenosine receptors (ADRs) A1 and A3, regulating the downstream PI3K/Akt and cAMP response element-binding protein (CREB) pathway and controlling the expression and phosphorylation level of Bcl-2 (Das, Cordis, Maulik, & Das, 2005). The activation of guanine nucleotide-binding protein-coupled receptors, such as ADR and opioid receptor (OPR), is known to repair I/R-induced damage in the heart. EGCG showed a cardioprotective effect by activating ADR, especially A (1) and A(2B) ADR, but not OPR in a Langendorff-perfused rat heart I/R model (Lee, et al., 2012).

Magnolol (Figure 1E), a phenolic acid extracted from *Magnolia officinalis*, has been showed to have a protective effect on I/R-induced injury models. In 2008, Jin et al. reported the anti-apoptotic effect of magnolol in vivo via the extracellular signal-regulated kinase 1/2 pathways in a rat I/R injury model (Jin, et al., 2008).

Caffeic acid (Figure 1F), a hydroxycinnamic acid found in fruits, grains and dietary supplements, is known to protect cardiac cells from isoproterenol-induced apoptosis related to cardiac enzymes, antioxidants and lipid peroxidation (Kumaran & Prince, 2010).

α -Mangostins (Figure 1G) is a polyphenolic xanthone extracted from the mangosteen fruit (*Garcinia mangostana*). α -Mangostins can ameliorate isoproterenol-induced ultrastructural and functional abnormalities in the mitochondria, due to their ability to quench free radicals and activate the NO pathway (Sampath & Kannan, 2009).

Insights into the effects of flavonoids and their mechanisms in myocardial cell protection have emerged in recent studies. Luteolin (3,4,5,7-tetrahydroxyflavone, Figure 2G), belonging to the flavone subclass, has long been used in traditional

Chinese medicine for the treatment of various diseases. Luteolin is known to reduce the myocardial infarct size, strengthen contractile function and attenuate cardiomyocyte apoptosis in both normal and diabetic rats with I/R injury. The anti-apoptotic effect mediated by luteolin is associated with the regulation of the PI3K/Akt, ERK/PP1a/phospholamban (PLB)/sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA2a) and Janus kinase (JNK) signalling pathways, the up-regulation of the anti-apoptotic proteins fibroblast growth factor receptor 2 (FGFR2) and leukaemia inhibitory factor (LIF), increases in Bad phosphorylation and a decreased Bax-to-Bcl-2 ratio (D. Sun, et al., 2012).

Baicalein (5,6,7-trihydroxy-2-phenyl-4H-1-benzopyran-4-one, Figure 2H) is one of the major flavonoids extracted from *S. baicalensis*. The biological activities of baicalein is partially due to its antioxidant effects. Baicalein mediates the opening of mitochondrial KATP and anion channels. Thus, pretreatment with baicalein at a concentration of 10 μM offered significant protection against I/R injury and doxorubicin-induced cardiomyocyte apoptosis (Chang, et al., 2013). Song L et al. showed that baicalein reduced myocardial I/R injury by inhibiting 12/15 lipoxygenase activity; sequentially activating ERK1/2/AKT; and inhibiting p38 mitogen-activated protein kinase (MAPK), JNK1/2 and NF- κ B/p65 (Song, et al., 2014).

As a free radical scavenger, quercetin strengthens cardiac function and attenuates cardiomyocyte apoptosis. The elucidated mechanisms are as follows: inhibition of the JNK and c-fos cascade (Wu & Gu, 2007); the up-regulation of phase 2 enzyme expression; and the regulation of ERK1/2, JNK, p38 and Akt phosphorylation and interleukin (IL)-1 β (Gutierrez-Venegas & Bando-Campos, 2010). Other flavonoids such as rutin, apigenin, myricetin, isoflavones, the phyto-oestrogen genistein and others have been found to exert an anti-apoptotic effect on cardiomyocytes by a direct antioxidant activity.

As a radical scavenger, EGCG is known to exert cardioprotective activity. Sheng R et al. reported the anti-apoptotic effect of EGCG on cardiomyocytes and its inhibitory effect on oxidative stress in cardiac hypertrophy induced by pressure overload (Sheng, Gu, Xie, Zhou, & Guo, 2007). Later, they found that EGCG significantly inhibited H_2O_2 -induced telomere attrition, telomeric repeat-binding factor 2 (TRF2) loss and p53 elevation in H9c2 cells. These results suggest that the anti-apoptotic effect of EGCG on cardiomyocytes is associated with a telomere-dependent apoptotic pathway (Sheng, Gu, Xie, Zhou, & Guo, 2010).

3.4 Enhancing myocardial metabolism

Excess fatty acids can impair the function of an ischaemic heart. In addition, fatty acid metabolism contributes to ischaemic heart injury. Approaches to enhance myocardial metabolism have been proposed. One involves increasing glucose uptake and decreasing the fatty acid levels. Another approach up-regulates glucose metabolism by increasing pyruvate dehydrogenase (PDH) levels (the rate-limiting enzyme for glucose oxidation). The latter strategy may lead to optimum energy metabolism in the heart and relieve symptoms of ischaemia (van der Schouw, et al., 2002). PA (Figure 1H) is a phenolic acid extracted from *S. miltiorrhiza*, with a structure typical of the class. PA was found to inhibit fatty acid oxidation and switch the energy substrate preference of the heart from fatty acids to glucose (Cao, et al., 2009). In addition, polyphenols were reported to prevent mitochondrial respiratory impairment perhaps via a decrease in oxidative stress and an increase in PGC-1 β expression (Charles, et al., 2013). This may also help enhance myocardial metabolism.

3.5 Pro-angiogenesis and cardiocyte regeneration

Therapeutic angiogenesis is widely recognized as an effective strategy for reducing ischaemic injury by promoting the growth of new vessels or the maturation of pre-existing vessels. Some natural plant products have been reported to exert pro-angiogenic effects.

The pro-angiogenic effect of resveratrol has been observed primarily in myocardial infarction models both *in vitro* and *in vivo* (Kaga, Zhan, Matsumoto, & Maulik, 2005) as follows: First, according to the human coronary arteriolar EC tube formation assay, resveratrol can significantly accelerate tubular morphogenesis, along with inducing HO-1 and vascular endothelial growth factor (VEGF) expression. Second, resveratrol increases thioredoxin (Trx)-1, HO-1 and VEGF expression in rat neonatal cardiomyocytes. Third, pretreatment with resveratrol (1 mg•kg⁻¹•day⁻¹) for 2 weeks reduces the infarct size in rats. Furthermore, the expression of Trx-1, HO-1 and VEGF increased after infarction in rats pretreated with resveratrol. In addition to the Trx-1–HO-1–VEGF pathway, several factors such as NO, NOS, NF- κ B and specificity protein (SP)-1 are also attributed to the pro-angiogenic effects of resveratrol, because the expression of these factors is altered after infarction (Kaga, et

al., 2005).

SMND-309, a novel metabolite of SalB, has been shown to enhance the migration, capillary-like structure formation and levels of VEGF, phosphorylated erythropoietin (EPO) receptor and phosphorylated STAT3 at doses of 3, 10 and 30 µg/mL. This indicates the significant angiogenic effect of SMND-309 on HUVECs. This is related to the up-regulation of VEGF via EPO receptor/STAT3 signalling pathways (Du, et al., 2013).

4. Potential molecules for treatment of IHD

Polyphenols have also been shown to retard vascular ageing and improve ageing-related endothelial dysfunction by inhibiting oxidative stress and inflammation, in turn reducing the incidence of myocardial ischaemia (Dal-Ros., et al., 2012; Idris Khodja, et al., 2012). Although polyphenols have multiple pharmacological effects beneficial against IHD, only a few will be developed for clinical practice. Both a high-purity single compound and a mixed natural product extract might help protect against IHD. Clinical studies are needed to compare the efficacy of the two types. Polyphenols represent an important source of drugs in the prevention and treatment of IHD.

5. Conclusion and future perspective

Natural products represent an important source of novel drugs. Accumulated data suggest the potential of many polyphenols in treating IHD by reducing myocardial oxygen consumption and/or increasing oxygen supply. Most polyphenols act by enhancing myocardial metabolism after I/R, inhibiting platelet aggregation and thrombosis, promoting angiogenesis or EC repair, protecting the remaining myocardial cells, restoring myocardial contraction, etc. Their beneficial effects and structural diversity make them potential candidates for the prevention and treatment of IHD.

However, some issues need to be addressed. Firstly, their safety in humans must be carefully evaluated. Although natural products are generally considered to be less toxic, their potential toxicity, particularly of derivatives and analogues, should not be underestimated. Secondly, although polyphenols are adequately water soluble, their bioavailability must be improved. Finally, the phenolic hydroxyl groups present in these compounds, which contribute to their potent antioxidant activities, are easily oxidizable, thus raising the question of their stability in druggability. In conclusion, polyphenols constitute a valuable class of natural products with potentials for treating IHD.

Polyphenols are considered to be of great medicinal value due to their pleiotropic properties and structural diversity. In particular, they are good candidates for the prevention and treatment of IHD, as they reduce myocardial oxygen consumption and/or increase oxygen supply, enhance myocardial metabolism after I/R, inhibit platelet aggregation and thrombosis, promote angiogenesis or EC repair, protect the remaining myocardial cells or restore myocardial contraction.

The efficacy and safety of STA-2, the complex of natural polyphenols extracted from green tea, in the management of chronic stable angina have been evaluated in clinical phase II and II b trials. STA-2 significantly relieved chronic stable angina, as indicated by the change in total exercise time (TET) and time to 1 mm ST-segment depression during exercise tolerance testing (ETT). It also showed good safety for further development. Further, the State Food and Drug Administration (SFDA) of China has approved the use of new polyphenols-containing drugs, such as salvianolic acids for the treatment of chronic angina. At present, it is widely used in clinical practice due to its good efficacy and safety. The potential effects and underlying mechanisms of polyphenols are under study, to guide clinical practice.

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Table 1. The pharmacological effects of polyphenols on myocardial ischaemia via a decrease in oxygen demand or an increase in oxygen supply

Polyphenols	Plant Origin	Classification	Effects and Mechanisms	References
Salvianolic acid A	<i>Salvia miltiorrhiza</i>	Phenolic acid	Induces myocardial infarction in rats; vascular reactivity in streptozotocin-induced diabetic rats; EETs mediate cardioprotection through MAPK signalling pathway; Yang 2011 protects against vascular endothelial dysfunction; inhibits PDGF-BB-induced vascular smooth muscle cell migration.	Wang 2009a, 2009b, 2013 Sun 2012
Salvianolic acid B	<i>Salvia miltiorrhiza</i>	Phenolic acid	Directly promote NO production in endothelial cells by overexpression of eNOS or by an increase in eNOS activity. Enhancing eNOS activity via phosphorylation at eNOS Increase oestrogen receptor alpha and Src-caveolin-1 interaction and activate Nrf2-driven pathways of different kinases	Yang et al., 2008; Pan et al., 2011 Klinge et al., 2008 Haskó., 2010; Ungvari et al., 2010
Resveratrol	Grape wine	and Phenolic acid	inhibitor Decrease the intracellular levels of the endogenous eNOS Enhances eNOS activity via SIRT1-mediated deacetylation of lysines 496 and 506 in the calmodulin-binding domain of eNOS	Thirunavukkarasu et al., 2007; Haskó., 2010; Ungvari et al., 2010 Mattagajasingh et al., 2007

				Nicholson et al., 2010; Wallerath et al., 2002
			Increase endothelial eNOS expression level	
Piceatannol	stilbenoid		Restoring the eNOS regulator dimethylarginine dimethylaminohydrolase, eNOS expression and activity in endothelial cells under high-glucose oxidative stress	Frombaum et al., 2011
Hydrolysable tannins	<i>Rhus coriaria</i> (Sumac)	Phenolic acid	Mediates endothelium-dependent vasorelaxant effect via COX pathway activation, TNF- α inhibition, eNOS activation and free radical and ROS scavenging	Beretta et al., 2009
			Reduces cardiac preload in rabbits with pressure overload and ameliorate left ventricular function by inhibition of the remodelling of the left ventricular collagen network associated with suppression of myocardial TNF- α and MMP-2 expression	Yao et al., 2004
Curcumin	<i>Curcuma longa</i> Linn. another	Curcumin	Induces isolated porcine coronary arteries relaxation through the action of NO, cGMP and adrenergic beta-receptor	Xu et al., 2007
Quercetin	Naturally Prevalent	Flavonoids	Increases the NO bioavailability (by inhibiting oxygen enzymatic sources, i.e., xanthine oxidase and NADPH oxidase; Avoids BH4 oxidation and eNOS uncoupling; Scavenges O ₂ and thus protects NO; Increases intracellular Ca ²⁺ concentrations, stimulates eNOS activity in a dose- and time-dependent manner),	Lopez-Lopez et al., 2004; Busse et al., 1984; Romero et al., 2009; Kuhlmann et al., 2005
Quercetin, 3'-O-methyl-quercetin, quercetin-3-O-glucuronide	Quercetin and its human		Increases S-nitrosothiols and nitrite concentrations, activates	Shen et al., 2012

quercetin aglycone	metabolic transformation		<p>AMPK and then induces eNOS activity in human aortic endothelial cells</p> <p>Causes slight reduction in eNOS and significantly reduces ET-1 expression Tribolo et al., 2013</p> <p>Modulating ROS production and eNOS activation, increasing endothelium-derived NO via PI3 kinase-dependent pathway, enhancing coronary flow Potenza et al., 2007</p> <p>Produces endothelium-dependent vasodilation at a concentration of</p>
Epigallocatechin gallate	Tea	Flavonoids	<p>1–50 µM by activating eNOS via a phosphatidylinositol 3-kinase-, PKA- and Akt-dependent pathway in rat aortic rings Lorenz et al., 2004</p> <p>Preserves bioavailability of NO by reducing the endogenous NOS inhibitor ADMA level Tang et al., 2006</p>
Monoacetyl-vitexin rhamnoside (AVR)	<i>Crataegus</i> species (Hawthorn, Rosaceae)	Flavonoids	<p>Improves myocardial perfusion in isolated heart models with phosphodiesterase (PDE)-inhibitory properties Schüssler et al., 1995</p>
API0134	Acanthaceae plant <i>Andrographis paniculata</i> (Buri. f.) Nees	Flavonoids	<p>Promotes the production of prostaglandin; increases the PGI2/TXA2 ratio; prevents granulocytes from producing free radicals; scavenges H₂O₂, O²⁻ and •OH; and inhibits the induced aggregation of washed human platelets Guo et al., 1996</p> <p>Increases NO and cGMP contents and SOD activity, Wang et al., 1997</p>

decreases

endothelin and lipid hydroperoxide contents and maintains

the

NO/endothelin balance

Table 2. The polyphenols play inhibitory role in the platelet aggregation process.

Polyphenols	Plant Origin	Classification	Mechanisms	References
			Inhibits the degradation of the κ B inhibitor ($I\kappa B\alpha$), attenuates tissue factor mRNA	Holmes-McNary M and Baldwin AS Jr., 2000
Resveratrol	Grape and wine	Phenolic acids	Inhibits COX-1 and modifies COX metabolite production to regulate platelet activation, and blocks the arachidonate-dependent synthesis of inflammatory agents such as thromboxane B ₂ , hydroxyheptadecatrienoate and 12-hydroxyeicosatetraenoate	Crescente et al., 2009
			Anti-platelet, modulates haemorrhology, induces cAMP	Fan et al., 2010
Salvianolic acid A	<i>Danshen</i>	Phenolic acids	Inhibits phosphoinositide 3-kinase leading to anti-platelet activation and anti-thrombotic effect	Huang et al., 2010
Salvianolic acid B	<i>Danshen</i>	Polyphenols	Interfering with the collagen receptor $\alpha 2\beta 1$. Inhibitory action in platelets on PKC-dependent NADPH oxidase activation	Wu et al., 2008 Pignatelli et al., 2006
Quercetin		Flavonols	Reduces Fyn kinase activity as well as the activation of Syk and phospholipase C	Wright et al., 2010
Procyanidins	Cocoa	Flavonols	inhibit the formation of leukotrienes, which act as vasoconstrictors and inflammation stimulants	Manna et al., 2000

Table 3. Polyphenols inhibit cardiac remodelling or prevent myocardial apoptosis

Polyphenols	Plant Origin	Classification	Effects and Mechanisms	References
Resveratrol	Grape and wine	Phenolic acids	Inhibits hypoxia-induced apoptosis in H9c2 cells via the SIRT1–FoxO1 pathway	Chen et al., 2009
			Regulates autophagy signalling in chronic myocardial ischaemia; suppresses increases in phosphorylated mammalian target of rapamycin (p-mTOR); and	Sabe et al., 2014
			decreases levels of p70 S6 kinase (P70S6K), lysosome-associated membrane protein (LAMP)-2 and autophagy-related gene 12-5 conjugate	
			Protects cardiomyocytes against anoxia/reoxygenation injury via the TLR4/NF-κB signalling pathway	Zhang et al., 2012
Magnolol	<i>Magnolia officinalis</i>	Phenolic acids	Protects cardiomyocytes from ischaemia and reperfusion injury-induced apoptosis via extracellular signal-regulated kinase1/2 pathways in rat in vivo	Jin et al., 2008
Caffeic acid	Fruits, grains and dietary supplements	Phenolic acids	Ameliorates cardiac damage in ISO-induced myocardial infarction by maintaining lipid peroxide metabolism due to its free radical scavenging and antioxidant effects, and inhibiting cardiac cell apoptosis related to cardiac enzymes, antioxidants and lipid peroxidation	Kumaran KS and Prince PS., 2010
Alpha-mangostins	Fruits	Phenolic acids	Ameliorates isoproterenol-induced biochemical and morphological changes in mitochondria, possibly mediated by the NO pathway and its ability to quench free radicals	Sampath PD and Kannan V 2009
Luteolin		Flavonoids	Regulating signalling pathways of PI3K/Akt, ERK/PP1a/PLB/SERCA2a and JNK signalling pathways, up-regulating expression of anti-apoptotic proteins FGFR2 and LIF, increasing BAD phosphorylation and decreasing the ratio of Bax to Bcl-2, resulting in an anti-apoptotic effect	Sun et al., 2012;
Baicalein	Scutellaria	Flavonoids	Protects against I/R injury and doxorubicin-induced cardiomyocyte	Chang et al., 2013

	baicalensis		apoptosis, by mediating the opening of mitochondrial KATP and anion channels Inhibits 12/15 lipoxygenase, activates ERK1/2 /AKT, inhibits p38 MAPK, JNK1/2, NF-kB/p65, reduces myocardial ischaemia/reperfusion injury	Song et al.,2014
Quercetin	Flavonoids		Blocks JNK and c-fos cascade, and up-regulates phase 2 enzyme expression, and expression of ERK1/2, JNK, p38, AKT phosphorylation and IL-1 beta gene	Wu et al., 2007; Gutiérrez-Venegas and Bando-Campos, 2010
Epigallocatechin gallate	Flavonoids		Exerts anti-apoptotic effect on cardiomyocytes by inhibiting the effect of oxidative stress in pressure overload-induced cardiac hypertrophy	Sheng et al., 2007

Figure Legends

Figure 1. The chemical structure, molecular formula and molecular weight of selected flavonoids. A: Chrysin; B: quercetin; C: rutin; D: hesperidin; E: pinocembrin; F: baicalein; G: 3'-O-methyl-quercetin; H: quercetin-3-O-glucuronide; I: genistein; J: daidzein; and K: catechins.

Figure 2. Chemical structures of phenolic acids and polyphenols. A: salvianolic acid A; B: salvianolic acid B; C: salvianolic acid C; D: salvianolic acid D; and E: resveratrol.

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