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Review

Flavonoids in myocardial ischemia-reperfusion injury: Therapeutic effects and mechanisms

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ABSTRACT

Ischemic heart diseases are one of the major causes of death worldwide. Effective restoration of blood flow can significantly improve patients' quality of life and reduce mortality. However, reperfusion injury cannot be ignored. Flavonoids possess well-established antioxidant properties; They also have other benefits that may be relevant for ameliorating myocardial ischemia-reperfusion injury (MIRI). In this review, we focus on flavonoids with cardiovascular-protection function and emphasize their pharmacological effects. The main mechanisms of flavonoid pharmacological activities against MIRI involve the following aspects: a) antioxidant, b) anti-inflammatory, c) anti-platelet aggregation, d) anti-apoptosis, and e) myocardial-function regulation activities. We also summarized the effectiveness of flavonoids for MIRI.

Contents

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1. Introduction

Among cardiovascular and other diseases, ischemic heart diseases are the leading cause of death. Ischemia–reperfusion (I/R)-induced tissue injury progress stepwise involving the ischemia and reperfusion phases (Fig. 1). During the ischemia phase, oxygen and nutrient deficiency impairs the expression of adenosine triphosphate synthase subunit delta (ATP5D), leading to a decrease in adenosine triphosphate (ATP) synthesis (Han, Li, Ma, & Fan, 2017). Furthermore, accumulation of hypoxanthine due to the metabolism of adenosine 5′-monophosphate (AMP) triggers the generation of peroxides (Bagheri et al., 2016). The peroxides damage DNA and cause lipid peroxidation, leading to the release of inflammatory cytokines (Bagheri et al., 2016). Leukocytes adhered to vessel walls release proteinases and peroxides, which increase vascular permeability, leading to the leakage of plasma albumin and red blood cells (Kumar et al., 2009; Rohrbach et al., 2015). The main white blood cells were CD11b- and CD18-positive polymorphonuclear cells (Liu et al., 2016a). The exposed vascular basement membrane promotes platelet aggregation and thrombosis (Rohrbach et al., 2015). In addition, CD4-positive lymphocytes extravasate and initiate a chronic inflammatory process (Liu et al., 2016a).

Flavonoids are aromatic keto-compounds found in several natural edible products, such as vegetables, fruits, legumes, and tea (Wang et al., 2018). They are of great therapeutic value, owing to their antioxidant, anti-inflammatory, antiviral, anticancer, and anti-ageing properties. Flavonoids have also been implicated in liver protection, immunity enhancement, and cardiovascular disease prevention (Brian et al., 1984). Specifically, they may prevent the generation of oxidants by chelating metal ions, inhibiting nicotinamide adenine dinucleotide phosphate oxidase (NADPH)

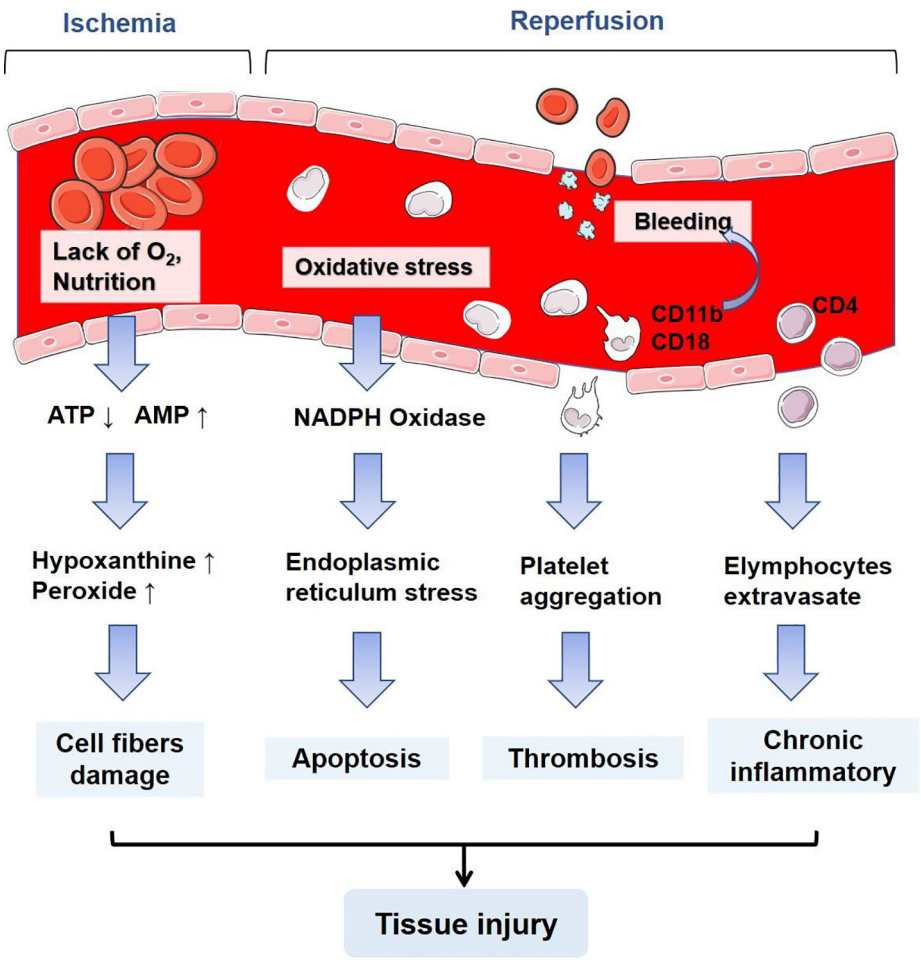

Fig. 1. Process of ischemia–reperfusion injury.

and lipid peroxidation, and inducing metabolic enzymes to improve the bioavailability of flavonoids. Additionally, flavonoids exhibit anti-inflammatory and antiplatelet-aggregation activities by suppressing the production of inflammatory cytokines, pattern-recognition receptors (PPRs), relevant enzymes, and oxidative stress-responsive transcription factors. Finally, flavonoids prevent mitochondrial injury, which induces apoptosis. These diverse activities of flavonoids reinforce their value as a potential therapeutic agent for MIRI. Moreover, several studies have verified flavonoid-induced cardioprotective effects in certain animal models or myocardial I/R cell lines. (An, Yang, & Ao, 2010; Ashafaq, Raza, & Khan, 2012; Daubney, Bonner, & Hargreaves, 2015; Gao, Ma, & Wang, 2014; F. He, Xu, & Chen, 2016; J.K. He, Yu, & Chen, 2010; Ji, Yue, Wu, & He, 2004; Kinoshita, Lepp, & Kawai, 2010; Lebeau, Neviere, & Cotelle, 2001; C. Li et al., 2014; D. Li, Wang, & Huang, 2018b; Liu, Ai, & Feng, 2016b; Panche, Diwan, & Chandra, 2016; Qiu, Cong, & Liang, 2017; Rao & Viswanath, 2007; Wang, Zhang, & Wu, 2013; Williamson, Kay, & Crozier, 2018; Wu, Nan, & Yang, 2018a; Yang, Yang, & Hu, 2015). Herein, we summarized the uses of flavonoids against MIRI and their therapeutic potential reported during recent years. We provide evidence of the cardioprotective effects of flavonoids, focusing on the major mechanisms of action, and the association between structure–activity relationship and cardiovascular health.

2. Chemical structure and classification of flavonoids

Flavonoids are a class of polyphenol secondary metabolites. They are widely present in glycosylated or esterified forms in plants (Lu et al., 2017; Wang et al., 2018). They consist of a 15-carbon skeleton, which comprises C6-C3-C6 rings, with rings A and B linked by a three-carbon ring C (Wang et al., 2018). The first oxygen atom in flavonoids is alkaline; therefore, they can form a salt by reacting with an acid (Sebastian et al., 2015). Flavonoids primarily have reductive properties; In humans, they are mainly oxidised by the CYPIA family members (Kinoshita et al., 2010). In the majority of flavonoids, the cross-conjugate double bond has a unique conformation, leading to yellow hydroxyl ramification, and hence the name of the compound (Williamson et al., 2018). Based on their chemical structure, specifically the degree of folding of the central three-carbon chain and the position of ring B, flavonoids can be classified as flavonols, flavones, isoflavones, flavanols, flavanonols, proanthocyanidins, anthocyanins, flavanones, and chalcones (Abotaleb et al., 2019; Biedermann et al., 2019; Kawaii et al., 1999).

2.1. Flavones

Flavones are a series of compounds formed by the interaction of two benzene rings (A and B rings) with phenolic hydroxyl groups via the central three-carbon atom. Their basic parent nucleus is a 2-phenylchromogenic ketone. Apigenin, a flavone, exhibited protective effect against MIRI in rats. It significantly reduced the malondialdehyde (MDA) level and enhanced superoxide dismutase (SOD) activity in MIRI. This indicated that apigenin can inhibit the peroxidation of free radicals and activate the activity of oxidase in the tissue to achieve the purpose of myocardial protection (Cheng et al., 2011). *In vivo*, wogonin, an *O*-methylated flavones, exerts cardioprotective effect by weakening the severity of ischemia-induced arrhythmia and irreversible I/R injury, which is related to the antioxidant capacity and anti-inflammatory effect (Lee et al., 2011). Luteolin can significantly reduce the release of LDH, incidence of arrhythmia, area of myocardial infarction, and rate of myocardial cell apoptosis; increase left ventricular ejection fraction; and protect the cardiac functions in diabetic rats after I/R injury (Sun et al., 2012). A previous study reported that the protective effect of orientin in H9c2 cells subjected to IR injury is associated with the suppression of mPTP opening, resultant mitochondrial dysfunction, and apoptosis (Lu et al., 2011). Tilianin can reduce lipid peroxidation-induced damage by increasing the activity of free radical-scavenging enzymes, in order to reduce the damage caused by lipid peroxidation on the biological membrane system of cardiomyocytes (Guo et al., 2013). Baicalin can reduce apoptosis via the PKCδ/p53 apoptotic signal pathway, and it plays a role in vascular protection under I/R injury (Shou et al., 2017). Breviscapine can significantly increase coronary blood flow, reduce CK and LDH release in outflow tract, inhibit myocardial histopathological changes, and protect the myocardium from I/R injury (Xu et al., 2005). Acacetin can reduce the expression of Bax and caspase-3, increase the expression of β-lymphoma-2 (Bcl-2), decrease the apoptosis of cardiomyocytes induced by hypoxia, and protect the myocardium from I/R injury (Wu et al., 2018b). Vitexin protected isolated rat heart from MIRI, and its action is related to the inhibition of inflammatory cytokine release and apoptosis of cardiomyocytes. It up-regulates the expression of Bcl-2 and down-regulates the expression of Bcl-2-related X protein (Bax) and NF-κBp65 (Dong, Fan, Shao, & Chen, 2011).

2.2. Flavonols

Flavonols are a kind of compound with hydroxyl or other oxygen-containing groups at position 3 of 2-phenylchromogenic ketone. The representative flavonols with an anti-myocardial ischaemic effect are quercetin, quercetin-3-glucoside, rutin, hyperin, kaempferol, fisetin, and morin. Quercetin treatment significantly alleviated the impairment of cardiac function following I/R. This protective effect was associated with improved mitochondrial function after I/R (Brookes et al., 2002). Quercitrin-3-glucoside exerted a protective effect against myocardial ischemia and hypoxia in mice, and this may be related to the improvement in anti-oxygen free radical-mediated lipid peroxidation (Liu & Chen, 2008). Rutin exerts cardioprotective effect, which is attributed to its peroxy radical-scavenging activity, and reduces I/R-induced cardiac dysfunction (Lebeau et al., 2001). The cardioprotective mechanisms of strong antioxidant flavonoids such as quercetin and myricetin have been elucidated. Although both protect the heart from IR injury, myricetin exerts a more pronounced protective action than quercetin owing to its capacity to inhibit STAT1 activation (Scarabelli et al., 2009). Hyperin can reduce MIRI and cardiomyocyte apoptosis in rats. The mechanism may be related to the formation of anti-oxygen free radicals and nitric oxide (NO) free radicals, and reduction in MIRI-induced apoptosis (Li et al., 2002). Kaempferol has protective effect against IR-related cardiac dysfunction. It can significantly improve the expression of the anti-apoptotic protein Bcl-2 and reduce the expression of endoplasmic reticulum (ER) stress proteins (Kim et al., 2008). Fisetin significantly attenuates IR-induced myocardial injury, reduces oxidative stress, and restores mitochondrial function by inhibiting glycogen synthase kinase 3β (Karthi et al., 2018). Morin can significantly improve cell viability, reduce LDH activity and apoptosis, improve cardiac function recovery, and reduce myocardial infarction area. Isorhamnetin pre-treatment can alleviate oxidative stress induced by doxorubicin and inhibit the activation of the mitochondrial apoptosis and mitogen-activated protein kinase pathways. Isorhamnetin exerted protective effect against doxorubicin-induced cardiotoxicity (Sun et al., 2012).

2.3. Isoflavones

Isoflavones had 3-phenyl chromone as the parent nucleus. In the process of MIRI in rats, daidzein can reduce myocardial injury,

indicating that it can reduce I/R-induced myocardial injury by inhibiting the activation of the transcription factor NF-κβ, thereby inhibiting the expression of inflammatory cytokines (Kim et al., 2009). The myocardial-protective effect of puerarin is related to the increase in NOS activity, which is inhibited in I/R myocardium. It exerted protective effect in the myocardium of I/R rats, and its action mechanism may be related to the activation of the PI3K/Akt signalling pathway (Ma et al., 2009). Genistein is a nonspecific inhibitor of tyrosine kinases, which are important mediators of ischemia preconditioning (Benter et al., 2005).

2.4. Flavanols

The structure of flavanols is characterised by the absence of carbonyl in the C-ring of 2-phenylchromonone and the hydrogenation of 2- and 3-position double bonds. The most frequently investigated flavanols are catechins, epicatechins, epigallocatechin, epigallocatechin gallate, and proanthocyanidins (polymeric catechins). Pre-treatment with epicatechin can inhibit the increase in metalloproteinase in myocardial infarction area, confirming that flavonoids can inhibit the activity of metalloproteinase in MIRI (Yamazaki et al., 2008). Epigallocatechin gallate inhibited the expression of NADPH oxidase subunit induced by angiotensin II in neonatal rat cardiomyocytes (Akhlaghi & Bandy, 2009).

2.5. Flavanonols

Flavanonols are a class of 2-phenyl chromogenic ketones with double-bond hydrogenation at the C2-3 position and hydroxyl group at the C3 position. Dihydroquercetin exerts a significant protective effect on MIRI *in vitro*, by improving the ability to scavenge oxygen free radicals and reducing the production of oxygen free radicals and damage of lipid peroxidation (Lu et al., 2017). Silymarin pre-treatment significantly reduces the MDA level in the myocardium, and CPK and LDH levels in the plasma. The protective mechanism of silymarin against adriamycin-induced toxicity is due to the inhibition of lipid peroxidation and protection of GSH depletion (El-Haggar & El-desoky, 2008).

2.6. Proanthocyanidins

Proanthocyanidins are complex flavonoid polymers, which are usually dimers or polymers of catechins and epicatechins. Proanthocyanidins exert an anti-oxidative effect in MIRI model rats. They can reduce the apoptosis of myocardial cells, and thus, reduce the area of myocardial infarction, in a dose-dependent manner (Zhang et al., 2012). Grape seed proanthocyanidin extract (GSPE) alleviates cardiac toxicity by inhibiting the expression of NOX, NOX2, and NOX4 (Tousson, Elgharabawy, & Elmasry, 2018).

2.7. Anthocyanins

Anthocyanins exist in plants in the form of ions and their basic structure is a glycosylated polyhydroxy or polymethoxy derivative of 2-phenylbenzopyran. Anthocyanins usually contain glycosyl groups attached to multiple positions or exist in the form of oligosaccharide side chains. Delphinidin can play a significant role in protecting the heart from I/R injury owing to its ability to inhibit STAT1 activation (Scarabelli et al., 2009). Luteolinidin is an effective CD38 inhibitor, and it can protect the heart from I/R injury, eNOS function, and endothelial dysfunction (Boslett et al., 2017).

2.8. Flavanones

Flavanones are a derivative of flavonoid C2-3 after double bond hydrogenation. Naringin can repair I/R injury by maintaining

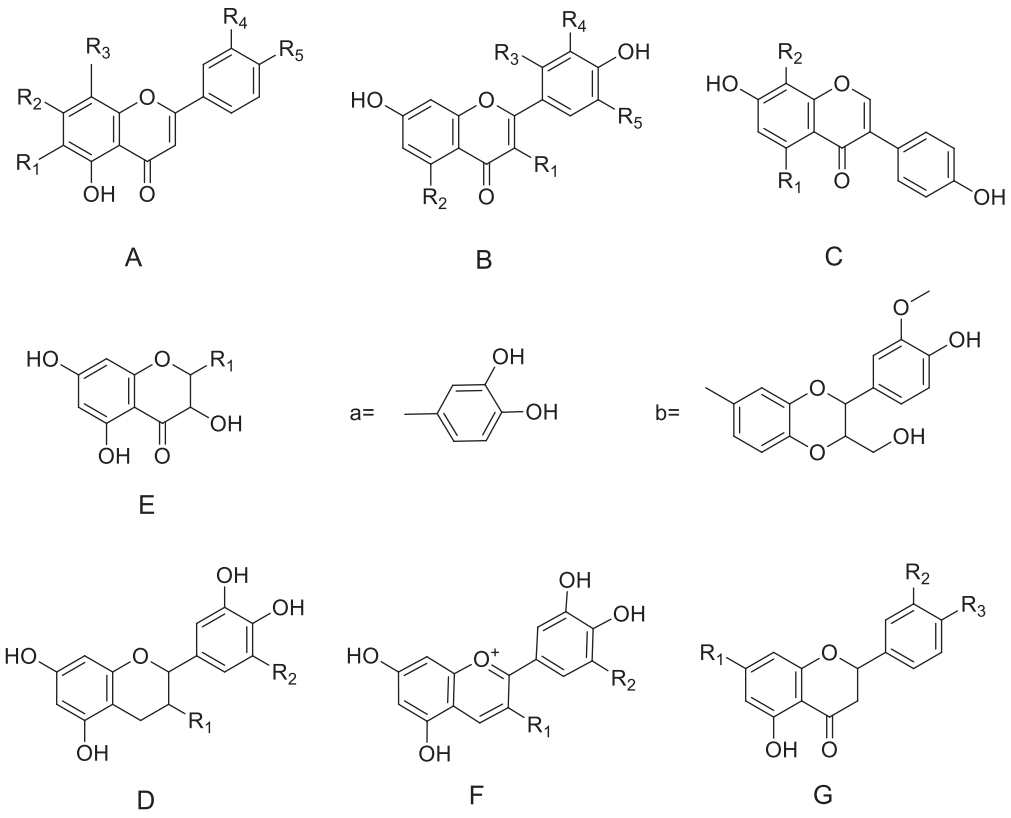

Fig. 2. Skeleton structures of active flavonoids. A: flavones; B: flavonols; C: isoflavones; D: flavanols; E: flavanonols; F: anthocyanins; G: flavanones.

myocardial structural integrity and regulating Hsp27, Hsp70, and p-eNOS/p-Akt/p-ERK signals and inflammatory response. It possesses antioxidant activity, which can alleviate I/R injury in the redox-sensitive myocardium (Lu et al., 2011). After treatment with hesperidin, the levels of nitrite and anti-oxidation in the heart tissue increased significantly, whereas inflammation, arrhythmia, and apoptosis decreased (Gandhi et al., 2009).

2.9. Chalcones

The three-carbon chain of the A and B rings of chalcone forms an open ring. Hydroxysafflor yellow A can inhibit the overexpression of TLR4 and reduce the cardiac damage caused by MIRI along with hyperlipidaemia (Han et al., 2016). The chemical constituents and structures of active flavonoids are shown in Fig. 2 and Table 1.

Table 1
Active flavonoid compounds.

Classification	No.	Compounds	Representive origins	Skeletons	R_1	R_2	R_3	R_4	R_5	Ref. Li et al., 2017b
Flavones	1	Apigenin	*Apium graveolens* L., *Matricaria chamomilla* L., *Reynoutria japonica* Houtt., et al.	A	H	OH	H	H	OH	Li et al., 2017b
	2	Wogonin	*Scutellaria baicalensis* Georgi., *Scutellaria barbata* D. Don., *Anodendron affine* (Hook. et Arn.) Druce., et al.	A	H	OH	OCH_3	H	H	Lee et al., 2011
	3	Luteolin	*Reseda odorata* L., *Dracocephalum moldavica* L., *Lonicera japonica* Thunb., et al.	A	H	OH	H	OH	OH	Zou et al., 2020
	4	Orientin	*Polygonum orientale* L., *Trollius chinensis* Bunge., *Phyllostachys nigra* (Lodd.) Munro., et al.	A	H	OH	Glu	OH	OH	Fu et al., 2006
	5	Tilianin	*Dracocephalum moldavuca* L., et al.	A	H	O-Glu	H	H	OCH_3	Guo et al., 2014
	6	Baicalin	*Scutellaria baicalensis* Georgi., *Houttuynia cordata* Thunb., *Scutellaria barbata* D. Don., et al.	A	OH	O-GluA	H	H	H	Shou et al., 2017
	7	Breviscapine	*Erigeron breviscapus* (Vant.) Hand.-Mazz., et al.	A	OH	O-GluA	H	H	OH	Ding et al., 2018
	8	Acacetin	*Acacia farnesiana* (Linn.) Willd., *Ziziphora clinopodioides* Lam., et al.	A	H	OH	H	H	OCH_3	Yang et al., 2014
	9	Vitexin	*Vitex negundo* var. *cannabifolia*., *Crataegus pinnatifida* Bge., et al.	A	H	OH	Glu	H	OH	Dong, Fan, Shao, & Chen, 2011
Flavonols	10	Quercetin	*Malus pumila* Mill., *Sophora japonica* L., *Hippophae rhamnoides* L., et al.	B	OH	OH	H	OH	H	Chen et al., 2019
	11	Quercitrin-3-glucoside	*Lophatherum gracile* Brongn., *Juniperus pingii* var. *wilsonii.*, *Houttuynia cordata* Thunb., et al.	B	O-Glu	OH	H	OH	H	Liu and Chen, 2008; Lin et al., 2011
	12	Rutin	*Ruta graveolens* L., *Crataegus pinnatifida* Bge., *Sophora japonica* L., et al.	B	O-Glu-Rha	OH	H	OH	H	Sclzuessler et al., 1995
	13	Myricetin	*Myrica rubra* Siebold et Zuccarini., *Ampelopsis grossedentata* Hand. -Mazz., *Xanthoceras sorbifolium* Bunge., et al.	B	OH	OH	H	OH	OH	Scarabelli et al., 2009
	14	Hyperin	*Hypericum monogynum* L., *Abelmoschus manihot* (L.) Medicus., *Crataegus scabrifolia* (Franch) Rehd., et al.	B	O-Gal	OH	H	OH	H	Li et al., 2002
	15	Kaempferol	*Kaempferia galanga* L., *Dracocephalum moldavica* L., *Thesium chinense* Turcz., et al.	B	OH	OH	H	H	H	Zou et al., 2020
	16	Fisetin	*Toxicodendron sylvestre* (Sieb. et Zucc.) O. Kuntze., et al.	B	OH	H	H	H	OH	Karthi et al., 2018
	17	Morin	*Morus alba* L., *Maclura pomifera* (Raf.) Schneid., *Maclura cochinchinensis* (Loureiro) Corner., et al.	B	OH	OH	OH	H	H	Liu et al., 2018
	18	Isorhamnetin	*Hippophae rhamnoides* L., *Ginkgo biloba* L., *Dracocephalum moldavuca* L., et al.	B	OH	OH	H	H	OCH_3	Li et al., 2015
Isoflavones	19	Daidzein	*Glycine* max (L.) Merr., *Trifolium pratense* L., *Pueraria montana* (Loureiro) Merrill., et al.	C	H	H	–	–	–	Kim et al., 2009
	20	Puerarin	*Pueraria montana* (Loureiro) Merrill., *Pueraria montana* var. *lobata*., et al.	C	H	Glu	–	–	–	Ma et al., 2009
	21	Genistein	*Genista tinctoria* L., *Sophora tonkinensis* Gagnep., et al.	C	OH	H	–	–	–	Benter et al., 2005
Flavanols	22	Epicatechin	*Theobroma cacao* L., *Xanthoceras sorbifolium* Bunge., *Lilium tigrinum* Ker Gawler., et al.	D	OH	H	–	–	–	Yamazaki et al., 2008
	23	Epigallocatechin gallate	*Camellia sinensis* (L.) O. Ktze., et al.	D	Gallate	OH	–	–	–	Stephanou et al., 2004
Flavanonols	24	Dihydroquercetin	*Larix gmelinii* (Ruprecht) Kuzeneva., *Pseudotsuga menziesii* (Mirbel) Franco., *Chamaecyparis obtusa* (Siebold et Zuccarini) Enelicher., et al.	E	a	–	–	–	–	Lu et al., 2017
	25	Silymarin	*Silybum marianum* (L.) Gaertn., et al.	E	b	–	–	–	–	El-Haggar and El-desoky, 2008
Anthocyanins	26	Delphinidin	*Consolida ajacis* (L.) Schur., *Astragalus mongholicus* Bunge., et al.	F	OH	OH	–	–	–	Scarabelli et al., 2009
	27	Luteolinidin	*Reseda odorata* L., *Sorghum bicolor* (L.) Moench., et al.	F	H	H	–	–	–	Boslett et al., 2017
Flavanones	28	Naringin	*Citrus paradisi* Macf., *Citrus maxima* (Burm.) Merr., *Vitis vinifera* L., et al.	G	O-Glu-Rha	H	OH	–	–	Rani et al., 2013
	29	Hesperidin	*Citrus reticulata* Blanco., *Citrus limon* (L.) Osbeck., *Citrus sinensis* (L.) Osbeck., et al.	G	O-Glu-Rha	OH	OCH_3	–	–	Roohbakhsh et al., 2015

3. Mechanisms of pharmacological activities of flavonoids against MIRI

Flavonoids protect against MIRI owing to their various biological activities. Recently, the number of studies on flavonoids in MIRI has been increasing. The mechanism of pharmacological activities of flavonoids against MIRI can be summarized as follows.

3.1. Antioxidant activity

It is well known that many flavonoids have antioxidant activity (Cherrak et al., 2016). Furthermore, the adjacent hydroxyl groups on the B chain are also vital for the antioxidant activity of flavonoids (He et al., 2018).

Several investigations have confirmed the antioxidant properties of flavonoids, and these properties may be related to their metal ion-chelating ability. Overloaded metal ions, such as iron, induce the production of active oxygen via the Fenton reaction, damaging the cytomembrane. However, flavonoids have a good affinity for iron and copper ions, and together they form inert compounds. Some studies have reported that rutin and quercetin can suppress redox-active labile plasma iron in both buffered solution and iron-overloaded sera. Both flavonoids are effective in loading the metal into the iron-transport protein transferrin. Iron derivatives of quercetin and rutin can permeate the cell membrane; However, only free quercetin can gain access to the cytosol and decrease intracellular labile iron pools (Baccan et al., 2012). Catechin, applied in perfusate, attenuated the increase in free iron in isolated rat hearts after anoxia and reoxygenation, and consequently, decreased hydroxyl radical formation via the Haber–Weiss and Fenton reactions (Modun et al., 2003).

Flavonoids can react with lipid free radicals or lipid-oxygen free radicals, which are intermediates produced during lipid chain oxidation, thus terminating the chain reaction and inhibiting lipid oxidation (Guo et al., 2014). Flavonoids are suspended on the surface of lipid-water membrane; Therefore, they have a strong inhibitory effect on induced peroxidation reaction (Tsuchiya, 2010). Yang et al. (2018) reported that proanthocyanidins, a class of flavonoids, protected against lipid peroxidation via the activation of the Nrf2 pathway and inhibition of the MAPK and NF-κB pathways, which were initially activated by oxidative stress. Apigenin significantly reduced the MDA level and enhanced SOD activity in MIRI, indicating that it could inhibit the peroxidation of free radicals and activate the activity of oxidase in tissues to protect the myocardium (Yang et al., 2018).

3.1.1. Inhibition of xanthine oxidase activity

Inhibition of xanthine oxidase (XO) activity is an important antioxidant mechanism of flavonoids to protect against MIRI. When tissue ischemia and hypoxia occur, ATP production is reduced, and membrane pumps fail, allowing excessive calcium ions to enter cells, activating calcium-dependent proteases, and converting xanthine dehydrogenase (XD) into XO in large quantities. Furthermore, due to ischemia and hypoxia, ATP is decomposed into ADP, AMP, adenosine, inosine, and hypoxanthine, whereas hypoxanthine is not metabolised to generate xanthine, making the substrate of XO to accumulate. During reperfusion, oxygen is resupplied to the ischemic tissue. During ischemia, a large amount of hypoxanthine is accumulated under the action of XO to form xanthine, which is then converted to uric acid. Both these steps use molecular oxygen as an electron acceptor, resulting in a large number of oxygen free radicals.

3.1.2. Inhibition of NADPH oxygenase

NADPH oxidase is a membrane-related enzyme that catalyses NADPH to accept an electron and react with oxygen. The expression and activity of NADPH oxidase subunits have been shown to aggravate myocardial infarction and cause myocardial injury, potentially leading to ventricular remodelling and myocardial thickening. This is because the ROS produced mediate several intracellular signalling pathways, such as mitogen-activated protein kinase pathway, Janus kinase-i signalling pathway, and transcriptional activator pathway, which are involved in the regulation of cell growth, division, differentiation, apoptosis, and senescence. Studies have demonstrated that flavonoids can inhibit enzyme activity and expression, such as epigallocatechin gallate, which can inhibit the expression of NADPH oxidase subunits induced by angiotensin II in neonatal rat cardiomyocytes (Akhlaghi & Bandy, 2009).

3.1.3. Induction of phase II enzymes

Phase II enzymes are known to eliminate toxic substances and electrophiles, and their expression is controlled by nuclear factor E2-related factor 2 (Nrf2). Nrf2 combines with antioxidant response element (ARE) in the nucleus to induce the expression of phase II enzymes (Li et al. (2017a); Ryter & Choi, 2016). Heme oxygenase-1 (HO-1), one of the phase II enzymes, inhibits ischaemic preconditioning and improves myocardial function (Forman et al., 2014). Some studies have shown that flavonoids can induce phase II enzymes in cultured human cells. Phase II enzymes, such as UDP-glucuronosyl transferases and glutathione, together with efflux transporters metabolise flavonoids and other drugs. Interestingly, their interaction increased the bioavailability and activity of flavonoids (Wen & Hu, 2012). Akhlaghi and Bandy (2010) studied the protective effect of 0.25% green tea extract flavonoids against MIRI in rats. The results showed that it can reduce MIRI-induced myocardial cell apoptosis and enhance GSH-px and phase II enzyme activities (Akhlaghi & Bandy, 2010). The steps involved in the oxidative stress processes and cardioprotective properties of flavonoids are shown in Fig. 3.

3.2. Anti-inflammatory activity

MIRI is considered a non-antigen-dependent inflammatory state induced by multiple factors (Zhang & Wang, 2014). PRRs, such as Toll-like receptors (TLRs), which are expressed in several immune and inflammatory cells, interact with endogenous and exogenous pathogens. Active TLRs are receptors whose endogenous ligands, such as high mobility group box 1 and heat shock proteins (HSPs), are formed during ischemia and reperfusion (Yu et al., 2010). HSP, a ligand of TLRs, is active during reperfusion and causes cardiomyocyte apoptosis. The activation of TLR increases the expression of chemokines and cytokines in cardiomyocytes. Flavonoids are known to inhibit TLRs and NLRP3 in cardiovascular diseases (Kim, Kwon, & Cho, 2012; Mozaffarian & Wu, 2018; Sun, Wang, & Zheng, 2016).

In addition, flavonoids exert inhibitory effects on a variety of pro-inflammatory factors such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), and inflammatory mediators such as PGE2, leukotriene, and NO. As flavonoids inhibit the transcription of phospholipase A2 cycloxygenase and inducible nitric oxide synthase (iNOS), they reduce the level of these inflammatory factors. Arachidonic acid (AA) is a well-known inflammatory mediator that produces leukotriene, prostaglandin E2 (PGE2), prostaglandin, prostacyclin, and thromboxane, which are inflammatory mediators and coagulants that induce a cascade of inflammatory reactions (Gross et al., 2005). AA negatively affects vascular endothelial cells and tissues, and it is catalysed by cyclooxygenase-2 (COX-2) and 5-lipoxygenase

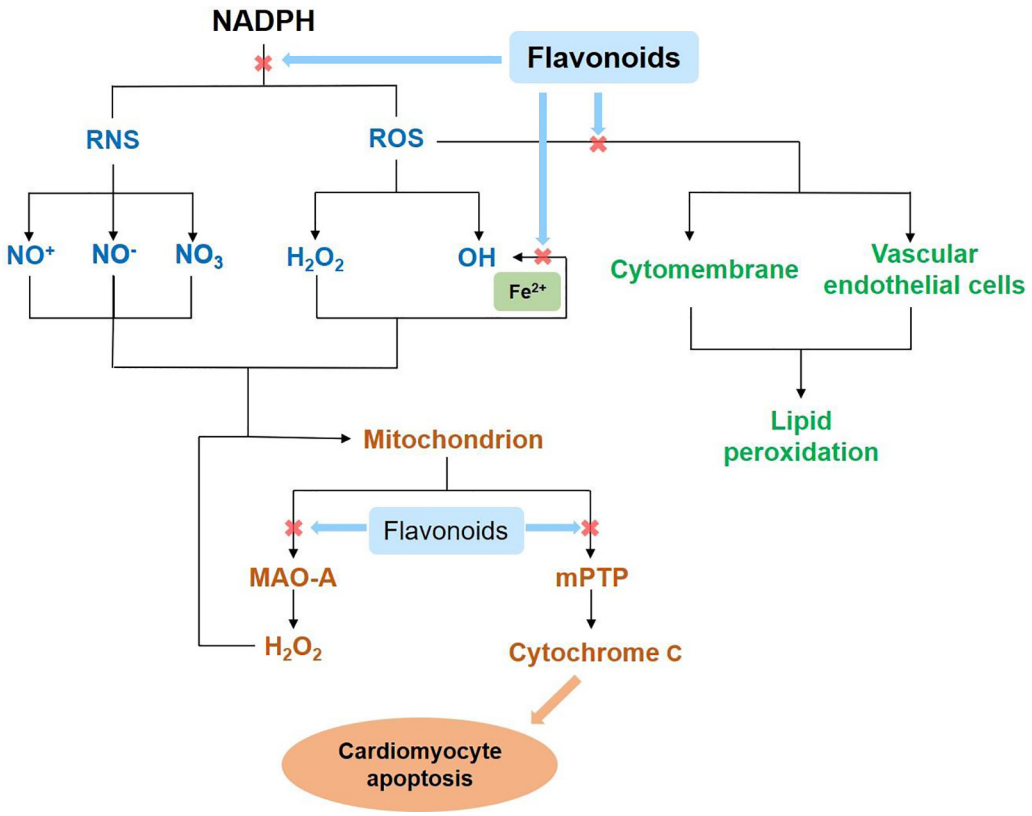

Fig. 3. Steps involved in the oxidative stress processes and cardioprotective properties of flavonoids. Flavonoids can be formed into inert compounds with metal ions to block the production of free radicals and can be antioxidant by blocking lipid peroxidation and inhibiting NADPH oxidase.

(Hanáková et al., 2017). Additionally, excessive NO could damage tissue. Inducible nitric oxide synthase (iNOS) is involved in the generation of NO. Cytokines also up-regulate the expression of iNOS. Flavonoids can exert anti-inflammatory effect by suppressing Inos (Gino et al., 2016). They can inhibit these two enzymes to exert anti-inflammatory effects (Werns & Lucchesi, 1988). Furthermore, puerarin, a class of isoflavones derived from Kudzu root (leguminous plant), exerts its anti-inflammatory activity by simultaneously inhibiting the NF-κB signalling pathway and suppressing IL-6 and TNF-α secretion (Fu et al., 2018).

Flavonoids also inhibit the expression of NF-κB, thereby reduce the expression of ICAM-1, VCAM-1, and E-selectin, and ultimately protect the structure and function of endothelial cells. NF-κB is an oxidative stress transcription factor activated by cytokines and inflammatory cytokines. TNF-α is a facultative cytokine found in different cells that can stimulate the secretion of a variety of inflammatory chemokines. Its excessive expression can induce inflammation (Suchal et al., 2016). TNF-α can activate NADPH oxidases to generate oxygen free radicals, which can accelerate the expression of NF-κB (Funakoshi et al., 2011). Flavonoids play the protective role of scavenging cytokines. Luo et al. (2015) reported that kaempferol suppressed inflammation by downregulating the expression of TNF-α, IL-6, and IκB kinase, and reducing the activation of the NF-κB pathway (Luo et al., 2015). Baicalin can upregulate the expression of HO-1. This lowers the level of NF-κB and decreases the expression of 1-κB, which exists in the nucleus during MIRI (Wang et al., 2016). Zhang et al. (2018) reported that dihydromyricetin exerts anti-inflammatory effect by reducing phosphorylation and by down-regulating NF-κB alpha, thus reducing p65 translocation into the nucleus and IκB kinase signalling; Consequently, TNF expression is inhibited (Zhang et al., 2018). These effects are attributable to the structural aspects of flavonoids, such as the location of the hydroxyl and alkoxy groups (Mattera et al., 2017).

Moreover, ROS stimulates the production of ONOO–, and then accelerates the expression of matrix metalloproteinases (MMPs), which are mainly distributed in the mitochondrion. MMP-2 promotes platelet aggregation. MMP-9 activates neutrophils in presence of an inflammatory insult. MMP-9 causes myocardial remodelling by degrading the extracellular matrix (ECM). It has been reported that luteolin can inhibit the activity of MMPs, contributing to the protective effect of luteolin to the reperfusion myocardium (Zhang et al., 2012).

3.3. Antiplatelet aggregation

The main function of platelets in the body is to clot and stop bleeding in order to repair broken blood vessels. When platelets are in the pathological state of over-activation, adhesion aggregation occurs, and thrombosis is promoted, which is the main pathological process of ischaemic heart and brain diseases, and thromboembolic diseases. Therefore, antiplatelet aggregation is particularly important in the prevention of such diseases.

Most natural flavonoids show anti-platelet aggregation effect, by inhibiting the formation of thromboxine A2 (TXA2) (Hodgson and Croft, 2010). In a healthy physiological state, TXA2 and prostacyclin (PGI2) maintain a dynamic balance in the coagulation system (Yang et al., 1993). During reperfusion, overproduction of TXA2 results in continuous platelet aggregation in vascular endothelial cells (Innes et al., 2013), leading to lipid peroxidation and free radical release. These radicals inhibit the release of PGI2. However, PGI2 typically inhibits platelet aggregation and promotes vasodilation. Some flavonoids, such as quercetin, catechin, and salvianolic acid A, have antiplatelet aggregation properties (Debnath

& Nath, 2014; Guerrero, NavarroNuñez, & Lozano, 2007). The possible mechanism involves their ability to control TXA2 and inhibit TXA2 receptors. Flavonoids stimulate PGI2 and increase cAMP concentration, which inhibits platelet accumulation (Akhlaghi & Bandy, 2009). Flavonoids may act as inhibitors of aggregation activated by AA (Faggio et al., 2017). Fan et al. (2017) demonstrated that 1, 2, and 4 mL/kg Danhong injection significantly increased the expression of PGI2 and PGE2 in rat models, leading to anti-platelet aggregation by inhibiting the GP IIb/IIIa receptor (Fan et al., 2017a).

Ca^{2+} overload in the cytoplasm and platelet granule secretion also play a key role in platelet aggregation. Studies have reported that quercetin inhibits platelet aggregation by suppressing Ca^{2+} activation and mitogen-activated protein kinase phosphorylation (Lopez et al., 2018). It has been reported that propolis extracts, which contain naringenin, kaempferol, quercetin, morin, and chrysin, could significantly inhibit platelet aggregation induced by TXA2. The underlying mechanisms involve the inhibition of phospholipase C, phospholipase A2, and cyclooxygenase 1 (COX 1) (Mirza et al., 2018). Wei et al. (2017) using a network pharmacological screening method, revealed the total flavonoids in *Hippophae rhamnoides*, with quercetin, isorhamnetin, kaempferol, pelargonidin, epicatechin, and cianidanol being the active compounds. They concluded that prostaglandin G/H synthase1, prostaglandin G/H synthase 2, β2 adrenergic receptor, and mitogen activated protein kinase 1 are associated with myocardium apoptosis, and that phosphatidyl inositol kinase CG, mitogen activated protein kinase 14, and interferon γ are associated with inflammation. They designed a 'compounds-targets-pathway' network to prove that Fc εRI and AA metabolism signalling pathways are related to platelet aggregation. Toll-like receptor, MAPK, JAK-STAT, leukocyte transendothelial migration, TGF-β, p53, and focal adhesion signalling pathway are associated with apoptosis (Wei et al., 2017). The action mechanisms of flavonoids in inflammatory and platelet aggregation-mediated I/R injury are shown in Fig. 4.

3.4. Anti-apoptosis

Recent studies have demonstrated that apoptosis is upregulated by ischemia and reperfusion (Morciano et al., 2015). Apoptosis plays a key role in MIRI. Flavonoids have a certain inhibitory effect on apoptosis and can significantly reduce the area of myocardial infarction. Liu and Feng (2010) used semi-empirical quantum chemical computation MOPAC-AM1 to explore the anti-apoptotic micromechanisms of flavonoids. They attributed the anti-apoptotic effect to hydroxyl groups on the carbon chain, and its strength to the presence of hydroxyl groups on the A and C rings. Because phenolic hydroxyl is stronger than alcohol-hydroxide, the hydroxyl groups on the B ring weaken their anti-apoptotic effect. However, this negative influence is offset by the hydroxyl groups on the A ring (Liu and Feng, 2010).

The possible mechanism is related to the inhibition of expression of pro-apoptotic genes (such as Bax) and the promotion of expression of anti-apoptotic genes (such as Bcl-2). Chahine et al. (2015) proved that 10 μg/mL saffron extracts (SAF), which contain flavonoids, prevented MIRI. Specifically, SAF activated AKT/P70S6K in H9c2 cells, inhibiting the caspase-3 activity (Chahine et al., 2015). In addition, the I/R injury resulted in the release of cytochrome *C* via mitochondrial permeability transition pore (mPTP) channel, which is made of protein complexes. Monoamine oxidase is located in the mitochondrial membrane, and contains two types, MAO-A and MAO-B, with MAO-A being the typical producer of H_2O_2. Flavonoids can inhibit the harmful effects of electron transport chain complexes (ETC) II, and MAO-A can prevent cardiomyocyte apoptosis. Cyclosporin A is an inhibitor of mPTP, which can inhibit the release of cytochrome *C* (Zhang et al., 2018). Further research should focus on whether flavonoids exert their anti-cardiomyocyte apoptosis effect directly through cyclosporin.

In addition, the interaction among some signalling molecules in the apoptotic signalling pathway is also beneficial to reduce the occurrence of apoptosis. Zhou et al. (2018) used H9c2 cells to evaluate the effect of apigenin against apoptotic myocardiocytes due to

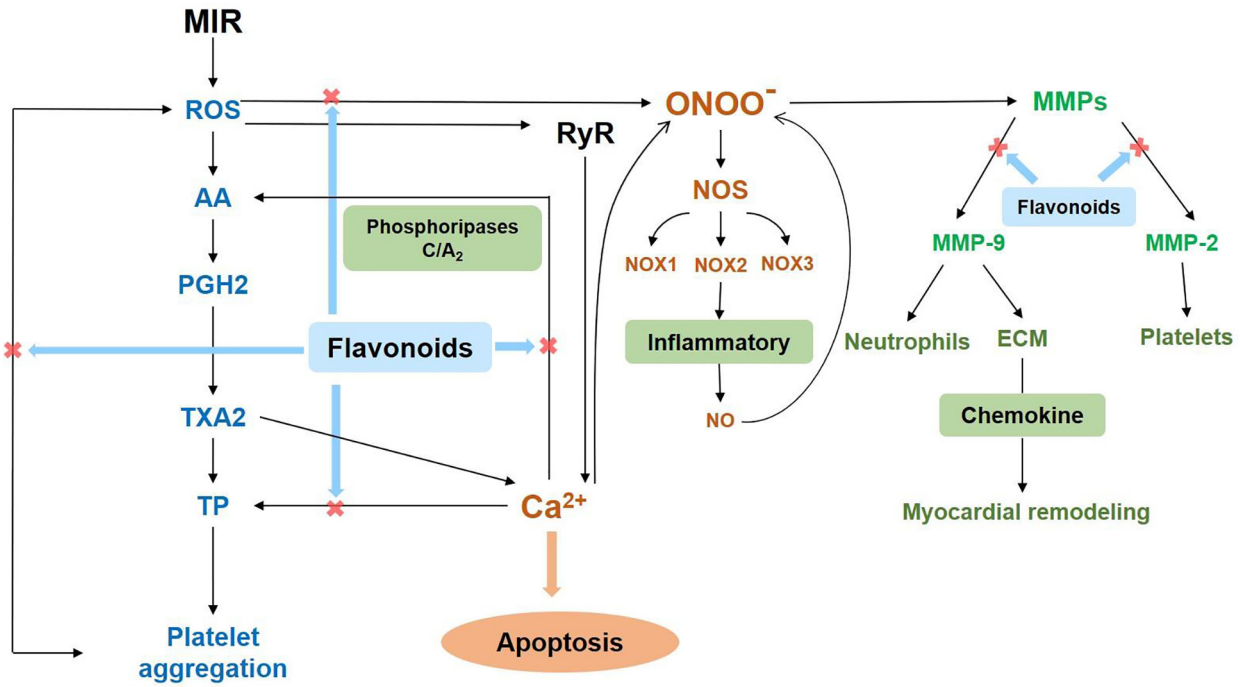

Fig. 4. The mechanisms of flavonoids in inflammatory and platelet aggregation-mediated ischemia–reperfusion injury. Flavonoids have anti-inflammatory effects mainly by affecting the secretion process and intercellular interactions of cells. Flavonoids play an anti-platelet aggregation effect mainly by inhibiting cyclooxygenase, reducing the generation of TXA2 and blocking TXA2 receptor, but also by reducing oxidative stress, reducing calcium overload.

MIRI. Their results showed that apigenin reduced ROS, the insult marker, and myocardiocyte apoptosis by up-regulating P13K/Akt (Zhou et al., 2018). In another study, Shanmugam et al. (2018) identified that fisetin, a type of flavonol, protected against MIRI by suppressing GSK3β signalling, specifically, by inhibiting oxidative stress and improving mitochondrial physiology (Shanmugam et al., 2018). The mechanisms underlying the anti-apoptotic I/R injury of flavonoids are shown in Fig. 5.

3.5. Regulating myocardial function

I/R negatively affects myocardial function through all the above-mentioned mechanisms. The weight of heart is less than 1% of the body. However, it needs 20% more blood than the whole body to sustain its activities. Examples of cardiac function indicators are left ventricular ejection fraction, left ventricular end diastolic diameter, cardiac output, and contractile function (Bao et al., 2018; De Jong et al., 2018; Hu, Guo, & Xi, 2016). Li et al. (2018a) found that cardiac function indicators, such as left ventricular pressure and left ventricular end diastolic pressure in rats after MIRI, were significantly decreased during treatment with eriodictyol (a flavanone) by activating the p-JAK2/JAK2 signalling pathways (Li et al., 2018a). Furthermore, Ikizler, Erkasap, Dernek, Kural, & Kaygisiz, 2007 evaluated the protective effect of intragastrically administered quercetin (most widely investigated flavonoids in cardiomyocytes) (Ikizler, Erkasap, Dernek, Kural, & Kaygisiz,

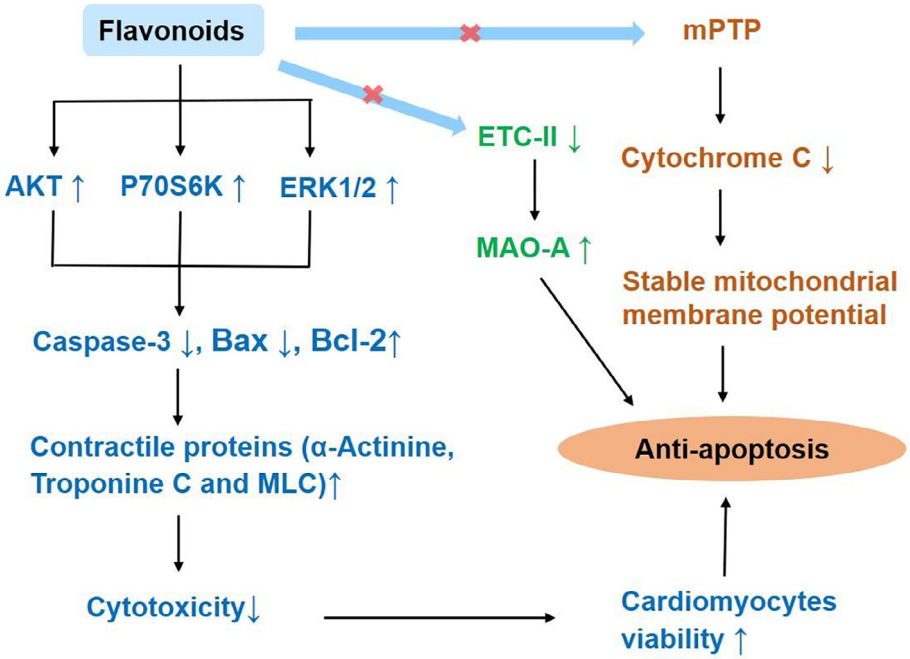

Fig. 5. Action mechanism of flavonoids in anti-apoptotic myocardial ischemia–reperfusion injury. Flavonoids inhibit caspase-3 and Bax activities, promote Bcl-2 expression, enhance cardiac contractile protein expression, reduce cytotoxicity, and improve cardiomyocyte viability by restoring the decrease in the phosphorylation of AKT, P70S6K, and ERK1/2. It can also inhibit the harmful effects of electron transport chain complex II (ETC-II), and MAO-A can inhibit cardiomyocyte apoptosis. Flavonoids can also reduce the release of cytochrome *C* during MIRI, stabilise mitochondrial membrane potential, and inhibit cardiomyocyte apoptosis.

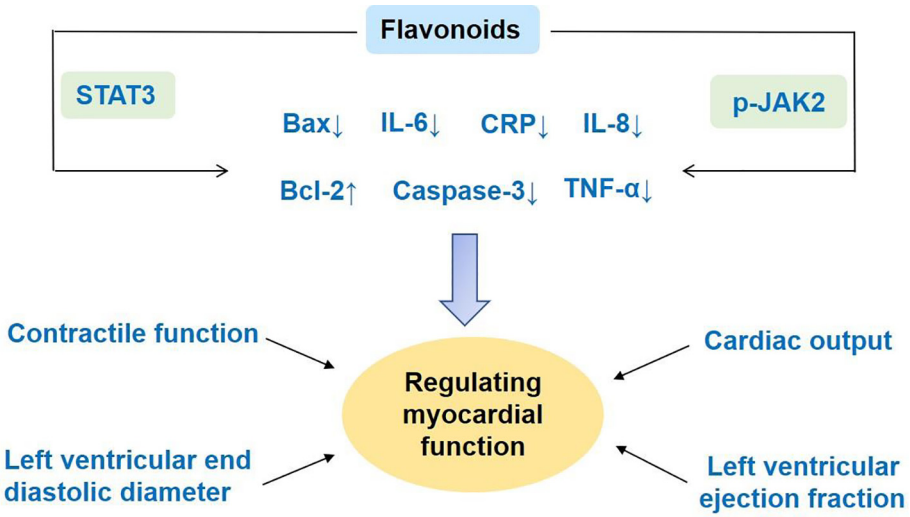

Fig. 6. Action mechanism of flavonoids in regulating myocardial function. Flavonoids inhibit caspase-3 and Bax activities, promote Bcl-2 expression, enhance cardiac contractile protein expression. By activating the p-JAK2 and STAT3 signalling pathways, regulating the cardiac function indicators such as left ventricular ejection fraction, left ventricular end diastolic diameter, cardiac output, and contractile function.

Table 2
Examples of some bioactive flavonoids against myocardial ischemia reperfusion injury.

Classification	Flavonoids	Doses	Models of reperfusion injury	Outcomes	Signaling pathways	Ref.Li et al. (2017b)
Flavones	Apigenin	50 mg/kg	H9c2 cells	cTnI↓, CMLC1↓, LDH↓, CK↓, TNF-α↓, IL-1β↓, MIP-1↓	NF-κB	Li et al. (2017b)
	Wogonin	5, 10, and 20 mg/kg	SD rats	p65↑, IkBa↑, caspase-3↑	MAPK	Cheng et al., 2011
	Luteolin	10 mg/kg	SD rats	FGFR2↑, LIF↑, Bax/Bcl-2↓, MPO↓, IL-6↓, IL-1α↓, TNF-α↓	PI3K/Akt	Sun et al., 2012
	Baicalin	10, 20, and 40 μmol/L	HAECs	PKCδ↓, p53↓, caspase-3C	PKCδ/p53	Shou et al., 2017
	Tilianin	2.5, 5, and 10 mg/kg/day	Rats	LDH↓, MDA↓, CK-MB↓, infarct size↓ SOD↑, SAD↑, Bcl-2↑	PI3K/Akt	Zeng et al., 2018
	Acacetin	0.3, 1, and 3 μmol/L	SD rats	Bax↓, TLR-4↓, IL-6↓ IL-10↑, Bcl-2↑, HO-1↑, Nrf2↑, SOD1↑, P38↑, AMPK↑	AMPK/Nrf2	Wu et al., 2018b
	Orientin	30 μmol/L	H9c2 cells	ROS↓, ΔΨm↓, Bcl-2↑, Bax↓	PI3K/Akt	Lu et al., 2011
	Breviscapine	10, 25 mg/L	Isolated rabbit hearts	CK↓, LDH↓		Xu et al., 2005
	Vitexin	50, 100, and 200 μmol/L	Rats	TNF-α↓, IL-6↓, Bax↓, Bcl-2↑	NF-κBp65	Dong, Fan, Shao, & Chen, 2011
Flavonols	Quercetin	30 μmol/L	H9c2 cells	TNF-α↓, ICAM-1↓, iNOS↓, IκB↑	JNK/SAPK	Angeloni & Hrelia, 2012
	Quercitrin-3-glucoside	2.5, 5, and 10 mg/kg	Rats	LDH↓, GSH-PX↑, MDA↓, SOD↑		Liu & Chen, 2008
	Myricitrin	2.5, 5, and 10 mg/L	SD rats	LDH↓, MDA↓, caspase-9↓, caspase-3↓, CK↓	PI3K/Akt	Chen et al., 2016
	Hyperin	25, 50 mg/kg	SD rats	CPK↓, MDA↓, SOD↑, NO↓		Li et al., 2002
	Kaempferol	0.01, 0.03, 0.1, 0.3, 1, 3, 10 and 30 μmol/L	H9c2 cells	Bcl-2↑, bax↓, GRP78↓, ATF-6α↓, XBP-2↓, IRE1α↓, phosphor-eIF-2α↓, CHOP↓	JNK	Kim et al., 2008
	Fisetin	20 mg/kg	Rats	GSH↓, LDH↓, CK↓, PARP↓ SOD↑, HO-1↑, NQR↑, SQR↑, QCCR↑, COX↑, mitochondrial membrane potential↑, mRNA↑ PGC1-α↑, NRF-1↑, TFAM↑	GSK3β	Shanmugam et al., 2018
	Morin	10, 20, and 40 mg/kg	Wistar rats	Infarct size↓, cytochrome c↓, APAF-1↓, caspase-9↓, caspase-3↓, LDH↓, MPTP opening↓, Bax/Bcl-2 ratio↓		Liu et al., 2018
	Isorhamnetin	5 mg/kg	SD rats	LDH↓, MDA↓, ΔΨm↓, Caspase-3↓	MAPK	Sun et al., 2013
Isoflavones	Daidzein	10 mg/kg	SD rats	TNF-α↓, IL-6↓	NF-κB	Kim et al., 2009
	Ginkgetin	100 mg/kg	Rats	CK↓, LDH↓, cTnI↓, MDA↓ SOD↑, beclin-1↑, LC3-II/I↑	NF-κB	Shen et al., 2016
	Soy isoflavone	30, 90, and 270 mg/kg/day	SD rats	CK↓, LDH↓, IS↓, iNOS↓ MDA↑	PI3K/Akt/eNOS	Tang et al., 2016
	Puerarin	0.3 mL/kg	SD rats	NOS↑, NO↑, cGMP↑	PI3K/Akt	Ma et al., 2009
Flavanonols	Dihydroquercetin	5, 10 mg/L	SD rats	CK↓, LDH↓, MDA↓, IS↓, SOD↑, GSH /GSSG↑		Lu et al., 2017
	Silymarin	60 mg/kg	Wistar rats	LDH↓, CK↓, XOD↓		El-Haggar & El-desoky, 2008
Flavanols	(-)-Epigallocatechin-3-gallate	100 mg/kg/day	SD rats	IS↓, LDH↓, MDA↓	SIRT1	Wu et al., 2017
	Epicatechin	1 mg/kg/day	SD rats	ROS↓, NO↓, GSH/GSSG↑		Yamazaki et al., 2008
Anthocyanins	Anthocyanin	10, 20 nmol/L	H9c2 cells	Bax↓, caspase-3↓, Bcl-2↑	JNK	Isaak et al., 2017
	Delphinidin	10, 25, and 50 μmol/L	SD rats	infarct size↓, caspase 9↓, caspase-3↓, CPK↓	STAT1	Scarabelli et al., 2009
	Luteolinidin	5, 15, 25, and 50 μmol/L	SD rats	CD38↓, percent infarct of the left ventricle↓ NADH↑, NAD+↑, BH4/BH2↑, left ventricular contractile function↑, CF↑	CD38	Boslett et al., 2017
Proanthocyanidins	Grape Seed Proanthocyanidin	50 mg/kg	SD rats	LDH↓, CK-MB↓, MDA↓, NOX2↓, NOX4↓, SOD↑		Tousson, Elgharabawy, & Elmasry, 2018
	Proanthocyanidin	50, 100, and 200 mg/kg	SD rats	CK↓, LDH↓, MDA↓, NO↑, SOD↑, GSH-Px↓, GSH↓, ROS↓		He et al., 2018
Flavanones	Naringin	20, 40, and 80 mg/kg/day	Rats	infarct size↓, LDH↓, CK-MB↓, TNF-α↓, GSH↓, GSH-px↓	TNF-α/IKK-β/ NF-κB	Rani et al., 2013
	Hesperidin	200 mg/kg/day	Rats	myocardial infarct size↓, CK-MB↓, cTnI↓, LC3II↓, Beclin1↓ p-mTOR↑, P-AKT↑, P-PI3K↑	PI3K/Akt/Mtor	Li et al., 2018

Table 2 (*continued*)

Classification	Flavonoids	Doses	Models of reperfusion injury	Outcomes	Signaling pathways	Ref.Li et al. (2017b)
Chalcones	Hydroxysafflor yellow A	8, 16, and 32 mg/kg	Wistar rats	myocardial infarct size↓, CK-MB↑, LDH↓, LPS↓, TNF-α↓, IL-1β↓	NF-κB	Han et al., 2016
	An Aza resveratrol-chalcone derivative 6b	50 mg/kg	Male C57BL/6 mice	col-1↓, mmp-9↓, tgf-β↓, myhc↓, TNF-α↓, CK-MB↓, IL-6↓	NF-κB	Huang et al., 2018
Total flavonoids	Total flavonoids of *Abelmoschus manihot* L. Medic.	40, 80 mg/kg	SD rats	CK-MB↓, IL-6↓, TNF-α↓, caspase-1↓, MDA↓, SOD↑	NLRP3	Lv et al., 2017
	Total flavonoids of Rhododendronsimsii	20, 40, and 80 mg/kg	Rats	UTR↓, RhoA↓, ROCK1↓, ROCK2↓, p-MLC↓	RhoA/ROCK	Luo et al., 2018
	Total flavonoids of *Dracocephalum Moldavica* L.	3, 10, and 30 mg/kg/day	SD Rats	CK-MB↓, MDA↓, LDH↓ Bcl-2/Bax↑	PI3K/Akt/GSK-3β	Zeng et al., 2018
	Total flavonoids of *Puerariae Lobatae* Flos.	20, 40, and 60 mg/kg	Wistar Rats	TNF-α↓, IL-6↓, IL-1β↓, AST↓, CPK↓, ATP↓, ADP↓, LDH↓, Bcl-2↑, Bax↓, caspase-3↓	NF-κB	Fan & Zhang, 2017
	Total flavonoids of Yinxing leaf	20, 40, and 80 mg/kg	Rats	MDA↓, SOD↑, LC3↓, beclin-1↓, CK↑, LDH↑, cTnI↑	NF-κB	Shen et al., 2016
	Total flavonoids of Uygur medicine bugloss	10, 30, and 50 mg/kg	SD rats	IL-1β↓、IL-6↓、TNF-α↓, Bcl-2↑, Bax↓	PI3K/Akt	Xu et al., 2014
	Total flavonoids of hawthorn leaf	50, 100, and 200 mg/kg	Wistar Rats	Bcl-2↑, infarct size↓, caspase-3↓, Bax↓		Gao et al., 2012
	Total flavonoids of *Cuscuta chinensis* Lam.	50, 100 mg/kg	SD rats	Bcl-2↑, Bax↓, caspase-3↓		Zhang & Wang, 2014
	Total flavonoids of *Bauhinia championii* Benth.	10, 20 mg/kg	SD rats	CK-MB↓, iNOS↓, LC3-II↓, Beclin-1↓, mTOR↑	NF-κB	Sun, 2015

2007). Quercetin ameliorated left ventricular pressure and poor left ventricular contractility. The action mechanisms of flavonoids in regulating myocardial function are shown in Fig. 6. Table 2 shows examples of some bioactive flavonoids against MIRI.

4. Discussion

4.1. Structure–activity relationship

The anti-myocardial ischaemic effect of flavone is also related to its hydroxylation structure. The hydroxyl substituent in the basic skeleton of flavone compounds is the active group that scavenges free radicals, and the substitution position and form of hydroxyl have an important influence on the activity. Xu et al. (2007) studied the structure–activity relationship of 17 natural flavonoids on vasodilation effect and found that the relationship between the skeleton structures and biological activity decreased in the following order: flavones > flavonols > isoflavones > flavanones (flavanonols) > chalcones > anthocyanidins > flavanes (flavanols) (Xu et al., 2007). It has been reported that the hydroxyl group in the B ring is the main active site of flavonoids for antioxidant and free radical scavenging (Wu et al., 2006). At this point, the more the number of hydroxyl substituents in the adjacent position, the stronger the antioxidant activity. The *ortho*-dihydroxyl groups in the A and B rings, especially 3′,4′-*ortho*-dihydroxyl substitution in the B ring, have a greater influence on the activity of flavonoids. The is due to the intramolecular hydrogen bonds formed by *ortho*-dihydroxyl groups stabilising free radicals, and it can result in the formation of *ortho*-benzoquinone to generate more stable free radicals. Methoxy substitution significantly improves cardiovascular protection probably by increasing the lipophilicity of flavonoids, thereby increasing the biofilm permeability. Flavonoid derivatives with methylene, methylene dioxyl, or allyl substitutions close to the chromogenic ketone skeleton often have a high pharmacological activity (Jiang et al., 2009).

4.2. Flavonoid compound-target-pathway-experimental model network.

The flavonoid compounds-targets-pathways-experimental models network was established using Cytoscape 3.7.1, as shown in Fig. 7. We collected and summarized the information of flavonoid compounds, targets and action pathways, and visualized the relationship between 46 compounds, 104 targets and 17 action pathways with myocardial ischemia through software processing. The nodes represent the compounds, targets, and action paths, and the edges are connected to represent the interaction between the targets and action pathways of the compounds. The larger the degree of connectivity is, the wider the network of nodes is. The importance of nodes in the network is reflected by the degree of intermediation, compactness, and connectivity. Through the analysis of nodes with a larger degree of connectivity in the network, it is found that the NF-κB signalling pathway and PI3K/Akt signalling pathway are the key nodes in the network, indicating that they may be the core pathway of flavonoids on myocardial ischemia. There was a "one-to-many, many-to-one" relationship between compounds and targets, and they reflected the anti-myocardial ischemia mechanism of flavonoids with multi-components and multi-targets.

4.3. Future perspective

Flavonoids are widely distributed in vegetables, fruits and medicinal plants, which have a variety of physiological activities related to cardiovascular protection and multi-target therapeutic advantages. Compared with western medicine like Trimetazidine

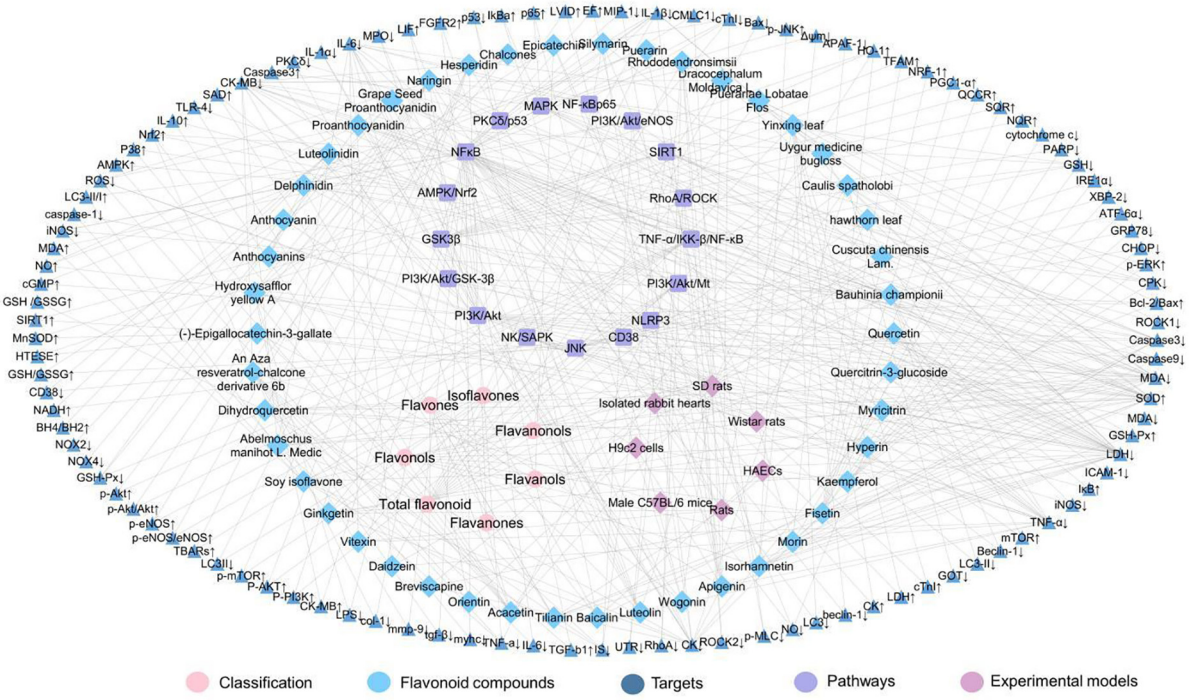

Fig. 7. Flavonoid compound-target-pathway-experimental model network.

and Simvastatin may have adverse effects such as gastrointestinal discomfort, flavonoids have fewer adverse effects in the treatment of MIRI. At present, rutin, hesperidin, puerarin and some flavonoids have been used as clinical drugs for cardiovascular system. *Ginkgo Folium*, *Scutellariae Radix*, *Puerariae Lobatae Radix* and other traditional Chinese medicines used in the cardiovascular system contain abundant flavonoids, which indicates that flavonoids have a good prospect in the treatment of MIRI. Although multiple mechanisms have been identified to elucidate how flavonoids protect the heart function, there are some limitations. Primarily, mPTP is an important therapeutic target to mitigating MIRI. There are many studies on the use of flavonoids to reduce mitochondrial injury, but the mechanism of mitochondrial outer membrane permeabilization (MOMP) which causes cardiomyocyte apoptosis is not deep enough. Moreover, the shape changes of mitochondria caused by fusion and fission can affect cell apoptosis, which shows that changing the shape of mitochondria may become a new target in the treatment of MIRI. Therefore, further research is needed to identify high-specific, high-efficiency, low-toxicity drugs and to provide valuable information for the search of a variety of drugs.

In addition, there is a need for large clinical trials designed to support the clinical utilisation of flavonoids, especially on the effective therapeutic dosage and safety of long-term treatment. Some experiments may be restricted by medical ethics. It is a challenge to translate reasonable experimental animal data to the clinical setting. Therefore, it is necessary to establish reasonable standards to evaluate the curative effect of flavonoids. Research on mechanisms should focus on target effectors and signalling pathways to distinguish the relationships and interactions of these effectors. In-depth evaluation and comparison of the protective effects of different types of flavonoids on MIRI, drug screening methods such as Structure-based drug design (SBDD) and Fragment-based drug design (FBDD) were used to search for the groups for pharmacological activity and try to make necessary structural modifications on the effective structures of active ingredients, such as active bonds, favorable substitution sites. It is of great scientific significance to find new targets of action, to discover new clinical uses of flavonoids, and to develop flavonoids anticardiac drugs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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