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Recent Advances in Natural Plant-based Treatment of Myocardial Ischemia-reperfusion Injury

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Abstract: Cardiovascular disease (CDV) is the primary cause of death in the world, and myocardial ischemia (MI) is one of the high-risk CVDs. The myocardial blood supply must be restored as soon as possible to reduce the mortality risk, however, reperfusion itself paradoxically leads to further death of cardiomyocytes and increases the infarct size; this is known as myocardial ischemia/reperfusion injury (MIRI). The pathological mechanism of MIRI is complex, and current research mainly focuses on oxidative stress, dysfunctional mitochondrial energy metabolism, Ca^{2+} overload, endoplasmic reticulum stress (ERs) and the inflammatory response. This review briefly summarizes the mechanism of MIRI, and natural plant product (NPP) components proven to ameliorate MIRI and their related signaling pathways. NPPs can alleviate MIRI by regulating oxidative stress, inflammation, ERs, Ca^{2+} overload and mitochondrial function maintenance. This review will deepen our understanding of how NPPs reduce MIRI and the future value of NPPs in cardio-protection.

Keywords: myocardial ischemia/reperfusion injury; natural plant products; mechanism; signaling pathways

1. Introduction

Cardiovascular disease is the leading cause of death all over the world; in 2019 it accounted for 18.6 million deaths, including 9.14 million deaths due to myocardial ischemia [1, 2]. In clinical settings, thrombolytic drugs and revascularization surgery are used to restore the blood supply of ischemic myocardium [3, 4]. However, the reperfusion paradoxically causes further cellular metabolic dysfunction, structural tissue injury, and even irreversible injury; this phenomenon is known as myocardial ischemia/reperfusion injury (MIRI). MIRI directly reduces the therapeutic effect of reperfusion and greatly increases the patient follow-up costs [5]. The pathological mechanism of MIRI is complex; it is associated with oxidative stress, mitochondrial dysfunction, Ca^{2+} overload and inflammation [6]. These factors cause damage to the myocardial intima, myocardial contractile dysfunction, and cardiomyocyte death [7]. Clinical treatment of MIRI is mainly focused on inhibiting the inflammatory response, reducing oxidative stress, preventing Ca^{2+} overload, and restoring energy metabolism [8-10].

Many natural medicines, especially natural plant products (NPPs), have multiple targets and low toxicity [11]. At present, a number of natural medicines have been found to exhibit therapeutic effects on MIRI, including glycosides, flavonoids, alkaloids, phenols, carbohydrates, terpenes, organic acids, amino acids and

catechins. These natural substances play a vital role in decreasing MIRI by inhibiting oxidative stress and apoptosis, reducing mitochondrial damage, and improving energy metabolism [9]. This article summarizes the latest papers on the treatment of MIRI with NPPs, and discusses the intervention effect of NPPs on MIRI through inhibition of Ca^{2+} overload, oxidative stress injury, mitochondrial damage, inflammatory response and other related mechanisms.

2. Mechanism of Myocardial Ischemia-reperfusion Injury

The mechanism of MIRI is related to oxidative stress, Ca^{2+} overload, energy metabolism disorder, inflammatory response, endoplasmic reticulum (ER) stress, apoptosis and autophagy. During ischemia, decreased oxygen and nutrient supply leads to energy metabolism dysfunction, resulting in the accumulation of reactive oxygen species (ROS) and Ca^{2+} overload, which can cause damage to cellular structures and organelles, such as mitochondria. When reperfusion begins, the sudden reintroduction of oxygen causes a surge in ROS and inflammatory responses, thereby exacerbating the MIRI. In addition, reperfusion injury impairs mitochondrial function, perpetuates ER stress, and leads to apoptosis and excessive autophagy. Various other factors also interact with each other in the process of MIRI.

2.1. Oxidative Stress

Under physiological conditions, the oxidants and the antioxidants system maintain a dynamic balance [12]. Ischemia/Reperfusion (I/R) progress produces excessive oxidants that break the balance between oxidants and the antioxidants. This phenomenon is called oxidative stress [13].

Elevated intracellular ROS level is an important characteristic of oxidative stress [14]. After the ischemic myocardium restores blood flow, oxygen molecules will produce a large amount of O_2^- under the catalysis of mitochondrial respiratory chain complex I and III, NADPH oxidase (NOX) and xanthine oxidases [12,15,16]. O_2^- is converted to H_2O_2 under the catalytic action of superoxide dismutase (SOD), and a large amount of H_2O_2 is also produced by the catalytic action of p66shc and monoamine oxidase isoforms (MAOs) [17, 18]. Due to large quantities, H_2O_2 cannot be completely detoxified by the peroxiredoxin/thioredoxin (PRX/Trx) system and glutathione peroxidase/reductase (GSH-PX) system; some H_2O_2 is converted to $\cdot OH$ under the catalysis of Fe^{2+} or to hypochlorite (HClO) by the catalytic action of myeloperoxidase [17,19].

ROS can directly damage the phospholipid bilayer of a cell membrane, leading to the imbalance of membrane components. Membrane fluidity and permeability are affected, which results in irreversible damage to organelles and cells [20]. Increase of ROS affects sarcoplasmic reticulum (SR), Ca^{2+}-ATPase (SERCA2a) and calcium-sensing receptor (CaSR), resulting in Ca^{2+} overload and myocardial contractile dysfunction [21]. Oxidative stress also causes the continuous opening of mitochondrial permeability transition pore (MPTP) during reperfusion, and the destruction of MPTP leads to mitochondrial rupture and damage, which affects cell energy metabolism [22]. ROS causes damage to DNA, which affects the correct synthesis of proteins, leading to cell death. Oxidative stress also causes an inflammatory reaction cascade; inflammatory factors are released and further reperfusion injury occurs [13].

Recent articles showed that NPPs could reduce MIRI by regulating related pathway proteins. For example, luteolin inhibits oxidative stress by inhibiting the mitogen-activated protein kinase (MAPK) pathway, and dihydroquercetin inhibits oxidative stress and reduces cardiomyocyte apoptosis by activating phosphoinositide-3 kinase (PI3K)/protein kinase B (AKT) pathway [23,24].

2.2. Ca^{2+} Overload

Ca^{2+} is mainly distributed in the mitochondria and the sarcoplasmic reticulum (SR) of the cell, and it is an important signaling molecule in excitation–contraction coupling (ECC) [25]. During myocardial ischemia, reduced synthesis of adenosine-triphosphate (ATP) decreases the activity of SERCA2a and intracellular Ca^{2+} accumulates, resulting in intracellular Ca^{2+} overload [26,27]. At the same time, during the ischemic phase, a large amount of H^+ is produced in the cell due to anaerobic respiration, resulting in a large amount of Na^+ entering the cell through H^+/Na^+ exchange (HNX) [28]. The excessive amount of intracellular Na^+ increases the activity of Na^+/Ca^{2+} exchange (NCX) proteins, which promotes Na^+ excretion and Ca^{2+} intake. The increased intracellular Ca^{2+} concentration leads to Ca^{2+} overload [29]. When reperfusion occurs, the

extracellular pH rises rapidly, further increasing HNX and NCX activity and exacerbating intracellular calcium overload [30]. Due to the presence of Ca^{2+} in the cytoplasm, the opening of ryanodine receptor 2 (RyR2) channels in the SR leads to Ca^{2+} influx from the SR into the cytoplasm, which also exacerbates intracellular Ca^{2+} overload [8]. Moreover, a large amount of ROS is generated during reperfusion, which damages the cell membrane. Altered cell membrane permeability then causes inward flow of Ca^{2+} and ER damage, which exacerbates Ca^{2+} overload [31].

During MIRI, a lot of Ca^{2+} accumulates in the cytoplasm. To maintain cytoplasmic Ca^{2+} homeostasis, mitochondria will take up excessive Ca^{2+} in the cytoplasm. This Ca^{2+} overload causes changes in mitochondrial membrane potential (MMP) and mitochondrial morphology [32,33]. Moreover, excessive Ca^{2+} in mitochondria inhibits ATP synthesis and disturbs mitochondrial energy metabolism [6, 25]. Intracellular Ca^{2+} also activates protein kinase A/phospholipase A, causing the breakdown of membrane phospholipids into free fatty acids, leukotrienes, ROS and other toxic substances, which causes changes in membrane permeability. Toxic substances also induce energy metabolism disorders and cell signaling, promoting apoptosis [34, 35]. Furthermore, Ca^{2+} overload causes structural and functional changes in coronary macrovascular and microvascular endothelial cells. These changes alter the vascular permeability, causing neutrophil adhesion, accumulation and infiltration, which release a series of inflammatory mediators that further damage the cardiovascular tissue [36,37].

Due to the close connection between calcium-related channel proteins and the apoptotic pathway, many NPPs inhibit Ca^{2+} overload by regulating Ca^{2+} channel protein-mediated apoptosis pathways, such as Astragaloside IV (AsIV), Hydroxysafflor Yellow A (HSYA) and total saponins of Aralia Elata [38-40].

2.3. Mitochondrial Dysfunction

Mitochondria is an important organelle that provides ATP and maintains energy metabolism [41]. The energy metabolism disorder caused by mitochondrial damage during reperfusion is an important mechanism leading to the death of cardiomyocytes [42]. MPTP opening is triggered by the anaerobic respiration, damage to the mitochondrial electron transport chain (ETC) during ischemia, mitochondrial Ca^{2+} overload, and excessive ROS [17,43]. The opening of MPTP leads to mitochondrial swelling and MMP loss [25,44].

During I/R, dysfunction in mitochondrial dynamics is a considerable cause of cardiac injury [45]. Under normal conditions, mitochondria fission and fusion depend on energy needs [46]. After I/R, the content of Mitofusion2 (Mfn2) in cardiomyocytes is decreased, while the content of dynamin-related protein 1(Drp1) is increased and translocated to the mitochondrial membrane, resulting in increased mitochondrial fission and decreased fusion [42]. The opening of MPTP not only reduces production of ATP, but also promotes the release of cytochrome c (Cyt c) and causes myocardial cell apoptosis [47]. Excessive fission leads to mutations in mitochondrial DNA fragments, aggravates Ca^{2+} overload and ROS burst [46].

Moderate mitophagy can eliminate damaged mitochondria and maintain mitochondrial quality, which is a significant way to reduce I/R [42]. During I/R, the depolarization of MMP causes the inhibition of the degradation process of PTEN-induced putative kinase 1 (PINK1), resulting in the accumulation of PINK1 on mitochondrial membranes [48,49]. Parkin is recruited to the mitochondria and attached to the site of ubiquitin protein through PINK1 on the mitochondrial membrane or through a PINK1-independent mechanism. The ubiquitinated mitochondrial protein is recognized by protein p62/sequestosome 1 and then linked to MAP1LC3 (LC3) on autophagosomes to engulf damaged mitochondria [50].

During the I/R process, the function, morphology, and dynamics of mitochondria are affected, resulting in cell apoptosis [42]. Mitochondrial damage is the result of multiple mechanisms, so there are many different therapeutic strategies for drugs that target mitochondria. Therefore, modulation of the damaged mitochondria during I/R includes modulation of electron transport, mitophagy and mitochondrial dynamic changes, inhibition of MPTP opening, Ca^{2+} overload and oxidative stress. For example, sappanone is a post-conditioning substance, which can reduce myocardial dysfunction and injury by regulating MPTP opening, mitophagy and mitochondrial dynamic via AMPK activation [51]. Moreover, Icariin could alleviate mitochondrial oxidative stress and apoptosis via SIRT1-dependent mechanism [52].

2.4. Endoplasmic Reticulum Stress

Endoplasmic reticulum (ER) is a very important organelle in eukaryotic cells; it maintains intracellular Ca^{2+} homeostasis, and synthesizes cholesterol and lipids. ER is also essential for protein synthesis, transport and modification [53, 54]. In physiological conditions, ER quality control system (ERQC) promotes the correct folding of proteins and degradation of misfolded peptides, which is regulated by folding enzymes, lectins and molecular chaperones [55]. During I/R, Ca^{2+} overload, oxidative stress and other factors will lead to ERQC dysfunction, causing the wrong proteins to accumulate, and eventually resulting in ER stress [56, 57]. In the early stage of ER stress, many chaperone genes are induced at the transcriptional level to clear accumulated unfolded proteins in time and to activate the ER-associated degradation (ERAD) system, which can send misfolded peptides to the cytoplasm for proteasome degradation. These processes are named unfolded protein response (UPR) [53,58].

UPR is regulated by a chaperone immunoglobulin/78 kDa glucose regulatory protein (BIP/GRP78) and three transmembrane signal sensors, namely, protein kinase-like ER kinase (PERK), activation of transcription factor 6 (ATF6), and inositol-requiring kinase 1 (IRE1) [54,59]. Under physiological conditions, the three transmembrane signal sensors bind to GRP78 on the membrane of the ER. During the URS, the misfolded proteins compete with the signal sensors to bind to GRP78, which triggers the signaling pathway of these three molecules [60]. Active PERK in turn activates the downstream signals, causing the decrease of protein translation and intracellular protein synthesis [55,61]. ATF6 is separated from GRP78 and degraded in the Golgi apparatus to produce active fragments. The active fragments enter the nucleus to promote expression of UPR target genes and then modify or regulate protein folding [62,63]. Active IRE-1 cleavages the X-Box Binding Protein 1 (XBP-1) mRNA gene precursor that activates ERAD and regulates protein translation [64]. In the early stage of ER stress, the activation of these three signaling pathways can protect the ER. However, continuous stress can aggravate oxidative stress and cell Ca^{2+} overload, which cause cell apoptosis and excessive autophagy [54,65].

Active ATF6, IRE1 and PERK promote the expression of the C/EBP homologous protein (CHOP). CHOP activates ER oxidoreductase 1(ERO1) to produce ROS [66]. c-Jun N-terminal kinase (JNK) is activated through the IRE1 pathway of the UPR and interacts with mitochondrial JNK-binding proteins, causing mitochondrial metabolism dysfunction and increasing level of ROS in mitochondria [67]. In addition, UPR leads to Ca^{2+} leakage from the ER and decrease of the Ca^{2+} absorption, which in turn leads to Ca^{2+} overload [68,69]. The mitochondria reuptakes the ROS and excess Ca^{2+} produced by the ER, however this leads to the production of more ROS in the mitochondria. ER stress aggravates Ca^{2+} overload and oxidative stress, which eventually leads to apoptosis [70,71]. Moreover, when UPR is activated, IRE1 activates the downstream nuclear transcription factor-κB (NF-κB), JNK and Recombinant X-Box Binding Protein 1 (XBP1) and cleaved ATF6, leading to the transcriptional activation of inflammation-related proteins; CHOP will also promote the release of proinflammatory cytokines. These factors contribute to the inflammatory reaction [72,73].

ER stress is mediated by oxidative stress, inflammation and Ca^{2+} overload, and ER stress will aggravate these pathological processes in turn. NPPs reduce MIRI by regulating ER stress-mediated signaling pathways，for example, Barbaloin pretreatment reduces MIRI by regulating the CNPY2-PERK apoptotic pathway [74]. Tournefolic acid B reduces MIRI by inhibiting PI3/Akt-mediated ER stress [75].

2.5. Inflammatory Response

During ischemia, inflammation is activated and further activated during reperfusion. Inflammation is an important cause of MIRI as it induces myocardial cell damage and affects myocardial function [76,77].

During myocardial ischemia, a lot of cell debris and inflammatory factors are produced. Cell debris and inflammatory factors are known as damage associated molecular patterns (DAMPs). Some DAMPs, such as ATP, single-stranded RNA, mitochondrial DNA, double stranded RNA, and complement factors, are recognized and bound to pattern recognition receptors (PRRs) to trigger inflammatory responses [78,79].

NLRP3 protein plays an important role in inflammasome activation. NLRP3 inflammasome, which is composed of NLRP3 receptor, apoptosis-associated speck-like protein containing a card domain (ASC) and Caspase-1, is a form of PRR and plays a vital role in inflammation caused by MIRI [80, 81]. NLRP3

expression is low under physiological conditions. During I/R, TLR ligands in cells are activated by DAMPs, which activate the NF-κB pathway through myeloid differentiation factor 88 (MyD88)-dependent or My88-independent pathways, and the activated NF-κB pathway in turn promotes the expression of NLRP3 [82-84]. DAMPs in cells can stimulate the assembly of the NLRP3 inflammasome and activate Caspase-1. Activated Caspase-1 promotes the cleavage of pro-IL-1β and pro-IL-18 into IL-1β and IL-18 respectively. IL-1β and IL-18 initiate an inflammatory cascade, which eventually leads to pyroptosis [85]. During reperfusion, myocardial cells produce ROS, which can activate the complement system and induce neutrophils accumulation in the infarct area. Cell adhesion molecules guide neutrophil migration to myocardial cells, leading to microcirculation obstruction. This promotes the production of proteolytic enzymes and ROS, thereby aggravating inflammation [86, 87]. In addition, ROS also induces neutrophils to produce a large amount of TNF-α, which activates the NF-κB pathway and promotes the release of inflammatory factors, such as IL-1, IL-6 and TNF-α, causing tissue damage [88]. Mitochondria plays a significant role in inflammatory response. Studies have shown that mitochondrial dysfunction and DNA leakage from broken mitochondria will activate the NLRP3 inflammasome and aggravate MIRI [89,90]. Moreover, Ca^{2+} overload is also an important factor in increasing the inflammation [91].

The inflammatory response is the result of the interaction of multiple factors and multiple pathways. At present, inhibiting the inflammatory response can be induced directly by inhibiting inflammation-related pathways. For instance, Cinnamic acid inhibits activation of the NLRP3 inflammasome and reduces MIRI [92]. In addition, Artemisinin can alleviate MIRI by inhibiting the production of ROS and the activity of the NLRP3 inflammasome [93].

2.6. Apoptosis

Apoptosis is a regulated form of programmed cell death; it is characterized by cell shrinkage, condensation of cytoplasm, nuclear shrinkage, and formation of apoptotic bodies [94]. Apoptosis is an important pathological mechanism involved in the entire MIRI process; it aggravates myocardial injury and leads to myocardial dysfunction [95].

Apoptotic pathways mainly include death receptor apoptosis pathway, mitochondrial apoptosis pathway, and ER pathway [96].

The death receptor apoptosis pathway refers to the process in which death receptors bind to related ligands on the cell surface, activates the caspase pathway, and triggers apoptosis. Death ligands are members of tumor necrosis factor (TNF) family, and receptors are members of tumor necrosis factor receptor (TNFR) family [97]. When the ligand binds to the receptor, it will activate caspase-8, which in turn activates downstream caspases, eventually causing cell apoptosis [96-98]. In the process of MIRI, the levels of TNF-α and TRAIL are increased, resulting in apoptosis.

Mitochondria plays a vital role in the process of apoptosis. After the apoptosis signal is activated, the permeability of the mitochondrial membrane will change, resulting in the leakage of Cyt c from the mitochondria into the cytoplasm. Cyt c activates Caspase-9, and then cleaves caspase-3, and finally triggers cell apoptosis [99]. The Bcl-2 protein family regulates apoptosis by controlling mitochondrial permeability. The anti-apoptotic proteins Bcl-2 reside in the mitochondrial outer membrane and inhibit the release of Cyt c, while the pro-apoptotic Bcl-2 proteins, Bax, can reside in the cytoplasm and translocate to the mitochondria after signal transduction, where it promotes release of Cyt c [100]. In addition, the loss of MMP and the burst of ROS will also cause the loss of Cyt c from mitochondria into the cytoplasm, triggering apoptosis [101].

ER stress is an important cause of apoptosis [54]. The excessive ER stress caused by I/R can increase the expression of CHOP protein, which in turn inhibits the expression of Bcl-2. ER stress also promotes the activation of Caspase-12 protein, eventually leading to apoptosis [102, 103]. In addition, Ca^{2+} overload and oxidative stress caused by ER stress also leads to apoptosis.

Apoptosis is the result of the interaction of multiple factors in the process of MIRI, and thus inhibiting cardiomyocyte apoptosis is also an important way to alleviate MIRI. At present, many NPPs can alleviate MIRI by inhibiting cardiomyocyte apoptosis. Dihydroquercetin could inhibit apoptosis via the PI3K/Akt pathway to reduce MIRI [104]. Resina draconis inhibits apoptosis via regulating the miR-423-3p/ERK signaling pathway [105].

2.7. Autophagy

Autophagy is a cellular process in which cells remove and recycle misfolded or damaged proteins and organelles through lysosomes [106]. It is associated with both cell survival and death, and plays an important role in maintaining the normal structure and function of the heart [107].

During myocardial ischemia, dysfunctional mitochondrial energy metabolism will cause the accumulation of large amounts of hydrogen ions and fatty acid through increased glycolysis, which will eventually lead to the inhibition of glycolysis process and fatty acid utilization. At this time, autophagy can promote the generation of ATP by fatty acids and amino acids in the cytoplasm through the tricarboxylic acid cycle [107,108]. Moreover, autophagy decreases apoptosis and protects the mitochondria membrane and cell membrane integrity [107,109].

However, during reperfusion, autophagy may have negative effects on cardiomyocytes, such as causing cardiomyocyte apoptosis. Excessive autophagy may affect cardiomyocyte energy metabolism and protein synthesis [108,110].

mTOR and Beclin-1 are the critical proteins in the autophagy process of MIRI. mTOR is mainly involved in the ischemic stage, and Beclin-1 is mainly involved in the reperfusion stage [107,111]. During ischemia, reduced ATP synthesis activates AMPK, which in turn inhibits the activation of mTOR through the AMPK-mTOR pathway [112]. In addition, autophagy can also be promoted through AKT-mTOR pathways [112]. During reperfusion, Beclin1 becomes the major mediator of autophagy. Although the upregulation of Beclin1 is responsible for autophagy activation during reperfusion, the mechanism by which cardiac I/R injury activates Beclin1 is still being studied [113]. One possible mechanism is its association with the Bcl-2 protein, which modulates Beclin1-mediated autophagic response to nutrient deprivation in cardiac cells [114]. ROS are also inducers of Beclin1 and mediates autophagy during reperfusion. Increased ROS generation is a major promoter of autophagy during this phase. Antioxidant interventions significantly suppress Beclin1 up-regulation, suggesting that ROS play a vital role in mediating Beclin1 upregulation [115,116]. During I/R, ER stress can lead to continuous UPR process and decreased Bcl-2 expression, and eventually lead to excessive autophagy [117].

Autophagy is a double-edged sword in the process of MIRI. NPPs can reduce MIRI by promoting or inhibiting autophagy. For example, Gastrodin can increase autophagy by regulating the AMPK-mTOR pathway to reduce MIRI [118], and Ginsenoside Rb1 can inhibit autophagy by regulating the PI3K/Akt/ mTOR pathway to alleviate MIRI [119].

3. Natural Plant Products in the Treatment of MIRI

3.1. Polyphenols

Polyphenols are a group of chemical substance; they contain multiple phenolic hydroxyl groups nad include more than 10,000 chemical compounds in a diverse variety of plants [120]. Polyphenols can be classified into different groups based on the number of phenol rings and the structural elements that bind these rings. They are classified into several subclasses, such as the lignans, stilbenes, flavonoids and phenolic acids [121,122]. In recent years, numerous biological activities and healthy benefits of polyphenols have been reported, including anticancer activity, antioxidant activity, heart protection effect and anti-inflammatory activity [120,123,124]. Besides, many studies showed that polyphenols are important in alleviating MIRI by regulating oxidative stress, inflammation and other mechanisms, as shown in Table 1.

Chen et al. [125] ligated the left anterior descending artery (LAD) in male Wistar rat to construct the I/R model. Carvacrol (CAR) was injected after ligation. The H/R model was established in vitro using neonatal rat cardiomyocytes (NRCs). The results showed that CAR administration had significant effects against oxidative stress and apoptosis. The results showed that CAR up-regulated the phosphorylation of extracellular-regulated protein kinases (p-ERK) and down-regulated the phosphorylation of p38 and JNK. The cardioprotective effect of CAR was reversed by the ERK inhibitor, indicating that the MAPK/ERK pathway was involved in the anti-apoptotic mechanism of CAR. In addition, pretreatment with CAR activated the Akt/endothelial nitric oxide synthase (eNOS) pathway in H/R cardiomyocytes in vitro, but the protective effect of CAR was abolished by the addition of an Akt inhibitor. These results suggested that the

Table 1. The cardioprotective effects of polyphenols in MIRI.

Compound	Model	Related pathway	Effects and mechanisms	Ref.
Luteolin	Vivo: ex rat MIRI model	p38 MAPK	Inhibiting MAPK pathway to reduce Ca^{2+} overload and restore the MMP.	[27]
Hydroxysafflor Yellow A	Vitro: NPCMs and hiPSC-CMs H/R model	LTCC	Regulating L-type calcium channel to inhibit calcium overload and apoptosis of cardiomyocytes.	[39]
Hematoxylin A	Vivo: ex rat MIRI model	AMPK	Through activation of AMPK signal pathway to regulate mitochondrial quality control that reducing mitochondrial dysfunction and MI.	[51]
Icariin	Vivo: ex rat MIRI model, mouse MIRI model Vitro: NRCs and H9c2 cells H/R model	SIRT1/FOXO1	Activating SIRT-1/FOXO1 pathway to alleviate oxidative stress.	[52]
Carvacrol	Vivo: rat MIRI model Vitro: NRCs H/R model	MAPK/ERK and Akt/eNOS	Inhibiting oxidant stress and apoptosis by regulating MAPK/ERK and Akt/eNOS signaling pathways.	[126]
Calendula E	Vitro: H9c2 cells oxidative damage model	———	Inhibiting ROS production in cardiomyocytes, maintaining the stability of mitochondrial energy metabolism.	[127]
Vitexin	Vivo: ex I/R model Vitro: H/R	Epac1	Inhibiting cardiomyocyte apoptosis by regulating Epac1 pathway to inhibit mitochondrial dysfunction.	[128]
Platycodin D	Vitro: H9c2 cells H/R model	Akt/Nrf2/HO-1	Inhibiting oxidative stress and cell apoptosis via regulating the Akt/Nrf2/HO-1 pathway.	[129]

Table 1. (Continued) The cardioprotective effects of polyphenols in MIRI.

Compound	Model	Related pathway	Effects and mechanisms	Ref
Gastrodin	Vivo: mouse MIRI model Vitro: NRCs H/R	AMPK-mTOR	Eliminating dysfunctional mitochondria by increasing autophagic flux	[119]
Ursolic-Acid	Vivo: rat ex MIRI model Vitro: H9c2 cells H/R model	———	Improving mitochondrial functional capacity and antioxidant status to protect myocardium during I/R.	[129]
Gastrodin	Vivo: mouse MIRI model Vitro: HCMECs H/R model	NLRP3/caspase-1 pathway	Inhibiting I/R-induced infammatory response by inhibiting NLRP3/caspase-1 pathway.	[130]
6-Gingerol	Vivo: rat I/R	PI3K/Akt	Inhibiting I/R-induced infammatory response via regulating the PI3K/Akt pathway.	[131]
Celastrol	Vivo: rat I/R	PI3K/ Akt	Reducing myocardial apoptosis, oxidative stress and inflammatory response by activating PI3K/ Akt pathway and inhibiting HMGB1pathway.	[132]
Emodin	Vivo: rat MIRI model Vitro: rat primary cardiomyocytes H/R model	TLR4/MyD88/NF-κB/NLRP3	Suppressing pyroptosis via inhibiting TLR4/MyD88/ NF-κB/NLRP3 inflammasome pathway.	[133]
Curcumin	Vitro: H9c2 cells H/R model	ERK/JNK	Increasing antioxidant activity and mitigating ERs and apoptosis via inhibition of ERK/JNK pathway.	[134]
Barbaloin	Vivo: rat MIRI model	CNPY2/PERK	Suppressing ERs-related apoptosis by inhibiting the cNPY2-PERK apoptotic pathway.	[135]

cardioprotective effect of CAR may be attributed to its antioxidant and anti-apoptotic activities through the regulation of MAPK/ERK and Akt/eNOS signaling pathways.

Tian et al. [126] treated H9c2 cardiomyocytes with H_2O_2 to establish an oxidative damage model. Pretreatment with calendula E (CE) analogue suppressed production of ROS, maintained MMP and inhibited cardiomyocyte apoptosis. Furthermore, CE analogues could increase the expression of B-cell lymphoma-2 (Bcl-2) and decrease the expression of Bcl-2-associated x protein (Bax) in a dose-dependent manner. These results suggested that CE analogues could protect H9c2 cardiomyocytes from H_2O_2-induced oxidative stress and apoptosis by inhibiting ROS production in cardiomyocytes and maintaining the stability of mitochondrial energy metabolism.

Yang et al. [127] established ex vivo I/R model and in vitro H/R models. The results showed that Vitexin (VT) inhibited production of ROS and the expression of exchange protein directly activated by cyclic adenosine monophosphate (cAMP) (Epac1) and Drp1. It also increased Mfn2 expression and MMP, thereby inhibiting myocardial cell apoptosis. These results suggested that VT inhibits cardiomyocyte apoptosis by regulating the Epac1 pathway to inhibit mitochondrial dysfunction.

Wang et al. [128] investigated the antioxidant effect and the underlying pathways of Platycodin D (PD) during I/R in H9c2 cells H/R model. The results showed that PD reduced production of ROS and malondialdehyde (MDA), and increased SOD production. Pretreatment with PD reduced the expression of Bax, cleaved caspase-3 and improved Bcl-2 expression. Furthermore, PD was found to induce the activation of Akt/nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase 1(HO-1) pathway, while the inhibitor of Akt reduced the effects of PD on the H/R model. These results indicated that PD pretreatment could inhibit H/R-induced cell apoptosis and oxidative stress by regulating the Akt/Nrf2/HO-1 pathway.

Wu et al. [52] constructed MIRI models of C57 mice and ex MIRI models of rat in vivo. H/R models of H9c2 cells and NRCs were constructed in vitro. After pretreatment with Icariin, it was found that Icariin could alleviate MI; inhibit cardiomyocyte apoptosis; restore cardiac function; reduce the level of lactate dehydrogenase (LDH), MDA and creatine kinase-MB (CK-MB); increase SOD content; and increase the expression of silent information regulator 1 (SIRT-1) and Bcl-2. Moreover, the expression of cleaved-caspase-3, acetyl-recombinant forkhead Box Protein O1 (Ac-FOXO1) and Bax protein decreased. However, the effect of Icariin was abolished by inhibitors of SIRT-1. These results suggested that Icariin protected against I/R-induced oxidative stress injury by regulating the SIRT-1/FOXO1 signaling pathway.

Shi et al. [51] used the Langendorff method to construct MI/R model and injected hematoxylin A (SA) before reperfusion. The results showed that SA postconditioning reduced myocardial infarct size, and inhibited LDH, CK-MB and cardiac troponin (cTnI) release. Other findings were that SA enhanced myocardial ATP production, enhanced mitochondrial complex activity, prevented loss of MMP and prevented opening of MPTP. In addition, SA treatment increased mitochondrial DNA (mtDNA) copy number and expression of peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α), Mfn2 and LC3-Ⅱ, however, it decreased the expression of Drp1. Adenosine monophosphate activated protein kinase (AMPK) antagonist could eliminate the protective effect of SA on the isolated heart. These results suggested that SA could reduce I/R induced-mitochondrial dysfunction and MI by regulation of mitochondrial quality control through activation of the AMPK signal pathway.

Fu et al. [117] constructed I/R model of C57 mice in vivo and NRCs H/R model in vitro to investigate the protective effect and potential mechanism of Gastrodin (GAS) during MIRI. The results showed that GAS could inhibit cardiomyocyte apoptosis. Expression of LC3Ⅱ and p-MAPK were increased, while expression of P62 and phosphorylation of the mechanistic target of rapamycin (P-mTOR) were reduced. The MMP was maintained. These results suggested that GAS reduced mitochondrial damage through autophagy and reduced I/R-induced apoptosis and tissue damage.

Yu et al. [129] explored the potential mechanisms by which ursolic-acid (UA) reduced MIRI in the H9c2 cells H/R model and rat ex MIRI model. The results showed that UA could enhance mitochondrial ATP synthesis and glutathione redox cycling to inhibit myocardial apoptosis. These results indicated that UA could protect the myocardium during I/R by improving mitochondrial functional capacity and antioxidant status.

Zhu et al. [27] explored the mechanism of Luteolin (Lut) in reducing Ca^{2+} overload during I/R in a rat ex MIRI model. The results showed that Lut increased the expression of phospholamban (p-PLB) and SERCA, and decreased the expression of p-MAPK. In addition, Luteolin could restore MMP and inhibit

apoptosis. These results suggested that Lut could enhance SERCA activity by activating p-PLB via inhibition of the MAPK pathway; ER reabsorption of Ca^{2+} improves, and mitochondrial damage caused by Ca^{2+} overload and apoptosis are inhibited.

Ye et al. [39] discovered HSYA could inhibit the sharp increase of the Ca^{2+} current induced by H/R, maintain the stability of intracellular Ca^{2+} concentration and reduce mitochondrial membrane potential by regulating L-type calcium channel (LTCC). HSYA could inhibit the expression of Bax and caspase-3 protein, and promote the expression of Bcl-2 protein. These results demonstrated that HYSA can alleviate MIRI through its inhibitory effect on Ca^{2+} overload and myocardial cell apoptosis.

Sun et al. [104] established the I/R model in male mice and the H/R model in human cardiac microvascular endothelial cells (HCMECs). Gastrodin (100 mg/kg/day) was injected intraperitoneally for 3 days before modeling. GAS (20, 40, 80, 100 μM) was given to the cells 2 hours before reoxygenation. The results showed that GAS pretreatment could increase the expression of VEGF protein in vitro and in vivo, while inhibiting the expression of IL-1β, NLRP3 and caspase-1 protein. GAS can also inhibit cell apoptosis and pyroptosis, and reduce myocardial infarction size. These results indicated that GAS could reduce the inflammatory response by inhibiting the NLRP3/caspase-1 pathway and myocardial tissue cell apoptosis to reduce myocardial injury.

Xu et al. [131] used MIRI model in SD rat. 6-gingerol (6-G) (6 mg/kg) was injected into the tail vein 30 minutes before LAD ligation. In the other group, 6-G (6 mg/kg) and a PI3/AKT inhibitor (LY) were administered via the tail vein 30 minutes before LAD ligation. 6-G preconditioning could reduce the area of myocardial injury and maintain physiological cardiac contractility. The level of TNF-α, IL-1β, IL-6 and CK-MB in serum were reduced. It also inhibited the expression of NLRP3, TNF-α, IL-1β and IL-6 in myocardial tissue and increased the expression of P-AKT and PI3. However, in the 6-G+LY group, the experimental results above were reversed. These results indicated that 6-G can inhibit IR-induced inflammation and reduce myocardial tissue damage through the PI3/AKT pathway.

Tong et al. [132] explored the relationship between triptolide and inhibition of I/R-induced inflammation in rat MIRI model. The results showed that Celastrol preconditioning could reduce myocardial infarction size. It can inhibit the expression of high mobility group box 1 (HMGB1), LC3, Beclin-1, Bax and p-AKT; increase the expression of Bcl-2; and reduce the level of inflammatory factors. However, the protective effect of Celastrol on myocardial tissue was reduced after adding a P13k inhibitor. The results showed that Celastrol alleviates myocardial I/R injury through the PI3K/Akt pathway to inhibit HMGB1 expression, thereby reducing myocardial apoptosis, myocardial autophagy and the inflammatory response.

Ye et al. [133] constructed a rat MIRI model in vivo and H/R model in vitro to investigate the effects of Emodin on MIRI. The expression of NLRP3 and its downstream inflammatory factors were significantly up-regulated in H/R-treated cardiomyocytes, while emodin pretreatment inhibited the expression of these proteins. Emodin also inhibited cell pyroptosis, improved cell survival rate in vitro and reduced myocardial infarction size in rat. These results indicated that emodin could inhibit the inflammatory response induced by H/R and inhibit pyroptosis.

Wei et al. [134] investigated the effect of Curcumin (Cur) on MIRI in H9c2 H/R model. The results showed that Cur inhibited cardiomyocyte apoptosis; decreased the level of LDH and MDA; and increased the level of SOD. Besides, Cur decreased the mRNA expression of GRP78 and CHOP, and the expression of GRP78, CHOP, p-ERK1/2 and p-JNK. These results demonstrated that Cur could reduce MIRI by regulating ER-related pathways and inhibiting oxidative stress.

Cui et al. [74] investigated MIRI in a rat model and showed that BAR could reduce MI, and reduce the expression of ER stress-related proteins (GRP78, CHOP, caspase-3/12, p-PERK, ATF4). In addition, BAR inhibited the mRNA expression of protein canopy homolog 2 (CNPY2) and GRP78. These results suggested that BAR could alleviate MIRI by inhibiting the CNPY2/PERK apoptotic pathway.

Jo et al. found that the effect of curcumin on MIRI is inconsistent. The experimental results showed that compared with the model group, curcumin administration could not significantly reduce the myocardial infarction area, because LDH, CK-MB and AST activity are still high. Futher more, curcumin could not effectively improve cardiac function [135]. In a study on Bifunctional Supramolecular Hydrogel in the context of MIRI, curcumin did not effectively inhibit autophagy and apoptosis caused by MIRI. However, curcumin embedded in the hydrogel had a good effect on alleviating MIRI [136].

3.2. Saponins

Saponins are a structurally diverse group of bioactive NPPs, and they are polar molecules, containing triterpene or steroid aglycone with one or more sugar chains [137, 138]. Many Chinese herbal medicines contain large amounts of saponins, such as *Panax ginseng* C. A. Mey, *Panax notoginseng* (Burk.) F.H. Chen, Panax quinquefolium L, Aralia elata (Miq.), and Astragali Radix [139-143]. In recent years, studies on saponins have found that they have antioxidant and cardiovascular protection properties, and can be used for treatment of neurological diseases [144, 145]. In addition, many studies have shown that saponins can alleviate MIRI, as illustrated in Table 2.

Table 2. The cardioprotective effects of saponins in MIRI.

Compound	Model	Related pathway	Effects and mechanisms	Ref
Astragaloside IV	Vivo: rat MIRI model Vitro: NRCs H/R model	CaSR/ERK1/2 and apoptotic signaling pathways	Reducing MIRI via regulating CaSR/ERK1/2 and related apoptotic pathways.	[38]
Total Saponins of Aralia Elata Seem	Vivo: rat MIRI model	———	Reducing ER stress, maintaining intracellular Ca^{2+} homeostasis and inhibiting cardiomyocyte apoptosis.	[40]
Asiatic Acid	Vivo: rat MIRI model Vitro: H9c2 cells H/R model	MAPK	Suppressing oxidative stress via regulating MAPK pathway.	[146]
Ophiopogonin D	Vivo: rat MIRI model	PI3K/Akt/eNOS, NF-κB	Inhibiting cell apoptosis and oxidative stress through regulating PI3K/Akt/eNOS and NF-κB pathways.	[147]
Ginsenoside Rb1	Vivo: rat MIRI model	RhoA	Modulating energy metabolism through inhibiting the activation of RhoA pathway.	[148]
Panax Notoginseng Saponins	Vivo: rat MIRI model	HIF-1a/BNIP3	Through activating HIF-1a/BNIP3 pathway to promote the mitochondrial autophagy.	[149]
Tilianin	Vivo: rat MIRI model	AMPK/SIRT1/PGC-1 α	Through regulating AMPK/SIRT1/PGC-1α pathway to maintain mitochondrial energy metabolism and reduce oxidative stress.	[150]
Curculigoside	Vivo: rat ex MIRI model Vitro: H9c2 cells H/R model	———	Maintaining MMP and inhibiting cell apoptosis via suppressing the opening of MPTP.	[151]
Notoginsenoside R1	Vivo: rat ex MIRI model Vitro: H9c2 cells H/R model	ERs related pathways	Alleviating MIRI by inhibiting the pathways of ERs and their related apoptosis.	[152]
Araloside C	Vivo: H9c2 cells H/R model	ERs-dependent apoptotic pathways	Inhibiting ERs-dependent apoptotic pathways by increasing HSP90 expression	[153]

Yi et al. [146] studied the mechanism by which asiatic acid (AA) is able to reduce MIRI in rat MIRI model and H9c2 cell H/R model. The results showed that AA could reduce the contents of MDA and ROS in serum and cells, and increase the level of SOD. The mitochondrial morphology and membrane potential were maintained. Reduction of cell apoptosis was achieved by inhibiting p38 and JNK phosphorylation; increasing Bcl-2/Bax ratio; reducing Cyt c release; and inhibiting the caspase cascade. These results suggested that AA

exerts cardioprotective effects through MAPK regulation of ROS-induced oxidative stress.

Huang et al. [147] constructed a rat MIRI model to investigate the mechanism of Ophiopogonin D (OP-D) in reducing MIRI. The results showed that OP-D could reduce myocardial injury, restore cardiac function and inhibit myocardial cell apoptosis in rat. OP-D treatment increased the expression of P-AKT and P-eNOS, and inhibited the expression of P-JNK. In addition, OP-D inhibited the expression of NF-κB in the nucleus. mRNA expression of Epoxyeicosatrienoic acids (EETs) and cytochrome P450 epoxygenase (CYPs) were increased. These results suggested that OP-D could alleviate cardiac injury after MI/R injury by regulating PI3K/Akt/eNOS and NF-κB signaling pathways to inhibit cell apoptosis and oxidative stress.

Cui et al. [148] investigated the effect of Ginsenoside Rb1 (Rb1) on rat MIRI model. The results showed that Rb1 treatment inhibited myocardial structural disruption, cardiomyocyte apoptosis, myocardial infarction and myocardial cTnI release induced by I/R. Rb1 also inhibited activation of the Ras homolog gene family member A (RhoA) signaling pathway and restored ATP production during myocardial I/R. In addition, surface plasmon resonance (SPR) experiments showed that Rb1 inhibited RhoA in a dose-dependent manner. The results suggested that Rb1 could restore mitochondrial energy metabolism and attenuate MIRI by regulating the RhoA signaling pathway.

Liu et al. [149] explored the relationship between Panax Notoginseng Saponins (PNS) and mitochondria by constructing a rat MIRI model. The results showed that PNS was able to reduce CK, MDA and LDH in serum and increase SOD in myocardial tissue. PNS treatment also increased the expression of hypoxia inducible factor (HIF-1α), Bcl2 interacting protein 3 (BNIP3), Beclin-1 and autophagy protein 5 (Atg5), as well as increasing the ratio of LC3 III/LC3I. In addition, PNS treatment improved mitochondrial morphology and inhibited cardiomyocyte apoptosis. The results indicated that PNS could alleviate MIRI by appropriately increasing the autophagic capacity of mitochondria and reducing ROS production.

Tian et al. [150] explored whether Tilianin was able to alleviate MIRI by regulating mitochondrial energy metabolism and oxidative stress through the AMPK/SIRT1/peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) signaling pathway in the rat MIRI model. The results showed that Tilianin could reduce myocardial infarct size and improve myocardial pathological morphology. It could increase levels of ATP and NAD^+; enhance SOD activity; and significantly increase AMPK, SIRT1 and PGC-1α mRNA levels. Meanwhile, it could decrease AMP/ATP ratio, MDA and ROS. The protein expression of AMPK, p-AMPK, SIRT1, PGC-1α, recombinant nuclear respiratory factor 1 (NRF1), recombinant transcription factor A, Mitochondrial (TFAM) and FOXO1 were up-regulated. However, these effects were inhibited by AMPK-specific and SIRT1-specific inhibitors, respectively; this suggests Tiliani alleviates MIRI through regulation of the AMPK/SIRT1/PGC-1α signaling pathway to maintain mitochondrial energy metabolism and reduce oxidative stress.

Zhao et al. [151] constructed rat ex MIRI model in vivo and H9c2 H/R model in vitro to investigate the effect of Curculigoside on MIRI. The results showed that pretreatment with Curculigoside significantly increased cell viability, inhibited cardiomyocyte apoptosis and reduced infarct size. Curculigoside also inhibited the opening of MPTP and maintained ΔΨm. In addition, curculigoside significantly reduced the expression of apoptosis-related proteins. Notably, the protective effect of curculigoside was abolished by the MPTP opener. These results suggested that curculigoside may prevent MIRI by inhibition of mitochondrial MPTP opening, MMP maintenance and cell apoptosis inhibition.

Yin et al. [38] found that AsIV pretreatment in NRCs H/R model could significantly improve cell viability and cardiomyocyte survival. Reductions were seen in lactate dehydrogenase (LDH) release, intracellular free calcium concentration ([Ca^{2+}]i) and expression of CaSR, while phosphorylation of ERK1/2 increased. Comparatively, in a rat model of MI/R, pretreatment with AsIV significantly reduced the area of cardiac injury and cardiomyocyte apoptosis. Reductions were seen in CK-MB and cTnI levels. These results suggested that AsIV alleviates MIRI by inhibiting the CaSR/ERK1/2-related apoptotic signaling pathway.

Wang et al. [40] used a rat MIRI model to investigate the effects and mechanism of saponins, found in *Aralia elata* (Miq) seem (AS), in the context of MIRI. The results showed that the AS could significantly reduce the myocardial infarction area, and the levels of LDH, CK and MDA. It increased the content of SOD, and restored Ca^{2+}-Mg^{2+}-ATPase, Na^+-K^+-ATPase, Serca2a and calcineurin (CaN). The expression of Bcl-2 was up-regulated and the expression of Bax was down-regulated in the same treatment group. These results

indicated that AS could reduce ER stress, maintain intracellular Ca^{2+} homeostasis, inhibit cardiomyocyte apoptosis and alleviate MIRI injury.

Yu et al. [152] investigated the cardioprotective effect of Notoginsenoside R1 (NGR1) on rat ex MIRI model and H9c2 cell H/R model. The results showed that NGR1 pretreatment could reduce myocardial injury, restore cardiac function and inhibit cell apoptosis. NGR1 decreased the expression of ER stress responsive proteins, including GRP78, P-PERK, ATF6 and IRE, and inhibited the expression of proapoptosis proteins, including CHOP, Caspase-12 and P-JNK. Moreover, NGR1 reduced ROS level and increased the activity of antioxidants. These results indicated that NGR1 could alleviate MIRI by inhibiting the ER stress-related pathways.

Du et al. [153] investigated the effect of Araloside C (AsC) on H/R-induced apoptosis in H9c2 cells H/R model. These results showed that pretreatment with AsC could inhibit the leakage of LDH and cell apoptosis. AsC also inhibited the activation of the PERK/eIF2α pathway and decreased the expression of CHOP and caspase-12. Additionally, AsC significantly increased the expression of HSP90. The suppression effect of AsC on ER stress-related apoptosis, caused by H/R, is blocked by an HSP90 inhibitor. In conclusion, AsC can reduce H/R-induced apoptosis through increasing HSP90 expression to inhibit ER stress-dependent apoptotic pathways.

3.3. Terpenoids

Terpenoids, also known as terpenes or isoprenoids, are the general term for compounds and their derivatives with an isoprene unit as the basic structural unit [154,155]. At present, there are more than 80,000 terpenoids, which are mainly extracted from plants and bacteria [154,156]. Many Chinese herbal medicines contain large amounts of terpenoids, such as Euphorbia lathyrism L, Rhizoma Alismatis and Salvia miltiorrh [157-159]. Terpenoids are anti-inflammatory, anti-oxidative stress, and regulate mitochondrial function [160, 161]. In addition, there have been many advances in the use of terpenoids in alleviating MIRI, as shown in Table 3.

Table 3. The cardioprotective effects of terpenoids in MIRI.

Compound	Model	Related pathway	Efficacies and mechanisms	Ref
Tanshinone IIA	Vivo: mouse MIRI model	lncRNA AK003290/ miR-124-5p	Regulating AK003290 and miR-124-5p pathways to inhibit apoptosis, oxidative and MMP loss.	[162]
Tanshinone I	Vivo: rat MIRI model Vitro: (t-BHP)-stimulated H9c2 cells model	RIP1/RIP3/MLKL, Akt/Nrf2	Inhibiting oxidative stress and inflammation via regulating RIP1/RIP3/MLKL and Akt/Nrf2 pathways.	[163]

Chen et al. [162] established an H/R model in H9c2 cardiomyocytes. Pretreatment with Tanshinone IIA (TSA) show inhibition of apoptosis of cardiomyocytes; reduction in the level of LDH, MDA and ROS; and increased MMP. Knockdown of AK003290 and overexpression of miR-124-5p reversed the anti-H/R effect of TSA. These results showed that TSA could improve MMP, inhibit oxidative stress, reduce cardiomyocyte apoptosis, and alleviated H9c2 cardiomyocytes injury indued by H/R, by regulating the lncRNA AK003290/ miR-124-5p pathway.

Zhuo et al. [163] used tert-butyl hydroperoxide (t-BHP) -stimulated H9c2 cell model and rat MIRI model to investigate the cardioprotective effect of Tanshinone I (TI). The results showed that TI could inhibit the phosphorylation of receptor interacting protein kinase 1 (p-RIP1), phosphorylation of the receptor interacting protein kinase 3 (p-RIP3) and phosphorylation of mixed lineage kinase domain-like (p-MLKL). Meanwhile, TI can increase the expression of Nrf2, HO-1 and other antioxidant related proteins; reduce ROS production; and reverse MMP loss in the in vitro model. In the in vivo MIRI model, TI could alleviate the degree of myocardial tissue injury; reduce the level of TNF-α, MDA and IL-6; and increase the level of SOD. These results suggested that TI could inhibit oxidative stress and cellular inflammation by suppressing RIP1/ RIP3/MLKL and activating Akt/Nrf2 pathways to protect the heart.

3.4. Alkaloids

Alkaloids are a class of secondary products that are widely present in plants. More than 12,000 different structures have been identified, most of which contain nitrogen atoms [167,168]. Alkaloids have a wide range of pharmacological activities and many of them have been applied in traditional or modern medicine [164]. In recent years, studies on alkaloids have found that they are anti-inflammatory, anti-cancer and anti-arrhythmic [165-167]. In addition, many studies have also proven that alkaloids have a significant effect on alleviating MIRI, and the main mechanism of this is through inhibiting myocardial cell apoptosis and improving mitochondrial energy metabolism, as shown in Table 4.

Table 4. The cardioprotective effects of alkaloids in MIRI.

Compound	Model	Related pathway	Effects and mechanisms	Ref
Berberine	Vivo: rat MIRI model Vitro: H9c2 H/R model	HIF-1α/ BNIP3	Improving mitochondrial energy metabolism and inhibiting oxidative stress by regulating AMPK/SIRT1/ PGC-1 α pathway.	[168]
Berberine	Vivo: rat MIRI model Vitro: H9c2 H/R model	JAK/STATS	Inhibiting ERs by activating JAK/STATS pathway to reduce MIRI.	[169]

Zhu et al. [168] explored the effect of Berberine (BBR) on MIRI by constructing an H/R model using H9c2 cells and rat MIRI model. In vitro, BBR pretreatment could regulate the expression of autophagy-related proteins, induce the production of autophagosomes and suppress the increase of MMP. In vivo, BBR reduced myocardial infarct size, inhibited cardiomyocyte apoptosis, and significantly reduced the level of CK-MB, LDH, and AST. In addition, the effect of BBR on MIRI was weakened after BNIP3 knockdown. Luciferase reporter and ChIP assays showed that BBR regulated BNIP3 expression through enhancing the binding of HIF-1α to the BNIP3 promoter. These results suggested that BBR moderately enhanced autophagy and inhibited cardiomyocyte apoptosis by regulating the HIF-1α/BNIP3 pathway, thus alleviating MIRI.

Zhao et al. [169] investigated the effect of BBR on MIRI by constructing a rat MIRI model and an H9c2 H/R model. The results showed that BBR pretreatment significantly reduced myocardial infarction size; maintained cardiac function; inhibited myocardial apoptosis; down-regulated phosphorylation of PERK and 65kDa eukaryotic translation initiation factor 2A (eIF2α); and down-regulated the expression of ATF4 and CHOP in cardiac tissues and H9c2 cells. In addition, pretreatment with BBR increased the phosphorylation of JAK2 and human signal transducer and activator of transcription 3 (STAT3). The inhibitory effect of BBR on ER stress and its cardiac protection effect could be abolished by JAK2/STAT3 specific inhibitor or transfection of JAK2 siRNA. These results suggested that BBR inhibited ER stress by activating JAK/STAT3 pathway to reduce MIRI.

4. Clinical Evidence

In view of the great potential of NPPs in reducing MIRI, clinical trials have been carried out to further verify whether certain NPPs can reduce myocardial injury following elective percutaneous coronary intervention.

Wongcharoen et al. [170] randomly divided 121 patients into two groups; one group received placebo and the other group received curcuminoids 4 g/day, in addition to standard therapy, from 3 days before coronary artery bypass grafting (CABG) to 5 days after CABG. The results showed that curcumin could significantly reduce CPR and MDA in serum, and reduce the incidence of left ventricular dysfunction and NT-proBNP. This proved that curcumin has the ability to reduce MIRI clinically. However, the study by Aslanabadi et al. [170] failed to support the ability of curcumin to alleviate MIRI. Aslanabadi et al. divided 110 patients into standard treatment group and intervention group. In addition to standard treatment, the intervention group were given oral administration of 480 mg nanomicelle curcumin before PCI. The results

showed that the intervention group did not have significant reductions in serum levels of CK-MB and cTn-I. Asgary et al. [171]. found that treatment with lycopene (30 mg 12 hours before PCI, 15 mg before PCI and 8 hours after PCI) added to the standard treatment group significantly reduced serum level of CK-MB, but did not significantly reduce level of cTn-I, compared to standard treatment. The study suggests that lycopene may alleviate MIRI. Aslanabadi et al. [172] randomly divided 99 patients into intervention group and control group. In the intervention group, 300 000 IU of vitamin D was taken orally 12 hours before PCI. The experimental results showed that vitamin D could not effectively reduce the serum levels of CK-MB and cTn-I when compared with the control group.

5. Discussion

5.1. Contradictions between Different Experiments

This review included 35 preclinical studies and 4 clinical studies. Thirty-three preclinical studies have shown that NPPs have the potential to alleviate MIRI, and two of them have inconsistent views. This may be related to the poor water solubility of the NPPs, especially curcumin. Embedding curcumin in the hydrogel increased the solubility of curcumin in water, and significantly improved the effectiveness of curcumin on MIRI [136].

Among the clinical research, we found that there were differences in experimental results. The studies of Wongcharoen et al. [170] and Asgary et al. [172] supported the role of NPPs in clinically reducing MIRI, however, Aslanabadi et al [171] and Aslanabadi et al. [173] could not support the effectiveness of NPPs in MIRI. It should be noted that the studies with positive experiemtnal evidence used larger doses of NPPs and had longer treatment periods. If the administration period of NPPs is short and the dose is low, it's difficult for NPPs to exert protective effects on the heart following PCI. Due to the lack of research on the active ingredients of NPPs, and the shortcomings in bioavailability and affinity of the active ingredients, the therapeutic effect of NPPs administration is slow [174]. Changing the dosage form of drugs may be necessary to achieve and maintain an effective blood concentration for therapeutic purposes [175].

At present, there is no good method to alleviate MIRI. Most of the studies mentioned in this article have involved pre-administration of the NPP for a long time before ischemia, due to the design of animal or cell experiments. Thus, NPPs can play a preventive role in MIRI and this has been proved in clinical practice. For example, curcumin can be administered before PCI to protect the heart, reduce the incidence of myocardial infarction, and reduce the level of biomarkers after PCI [170].

5.2. Limitation

The preclinical studies of NPPs to alleviate MIRI lack monitoring of cardiac function, so the experimental results cannot directly reflect the protective effect of NPPs on the heart. It may be necessary to conduct drug administration in animals after reperfusion and monitor the cardiac function of animals for a longer period of time in future preclinical studies.

At present, there are few clinical studies on the use of NPPs to alleviate MIRI. The research protocols of the above clinical studies are relatively simple, and there are few studies involving cardiac function tests. In the future, more clinical studies are needed to monitor the incidence of myocardial infarction and cardiac function for a longer time.

Experimental data is collected shortly after ischemia and reperfusion in most animal experiments and cell experiments, which means most experiments do not administrate long-term drug treatment after reperfusion. In summary, preclinical studies suggested that pretreatment with NPPs could protect the heart from I/R induced myocardial injury. However, there are some differences between the drug delivery methods in the studies and clinical drug delivery requirements; it is necessary to further explore drug delivery methods in animal models, in order to establish appropriate clinical drug delivery methods.

6. Conclusion

NPPs are multi-target compounds and they have shown great therapeutic potential. In recent years, many studies have been conducted on the use of NPPs to reduce MIRI. The composition of NPPs is complex,

and its anti-MIRI mechanisms are diverse. This review is mainly based on the material structure of NPPs and their mechanisms of alleviating MIRI. Some components of NPPs have anti-inflammatory and anti-oxidative properties, thus they can inhibit I/R-induced oxidative stress, Ca^{2+} overload, inflammation, mitochondrial dysfunction and ER stress. MIRI is the result of the interaction of multiple factors and multiple signaling pathways. The complex signaling molecular regulation of MIRI requires drugs that act on multiple targets and pathways. NPPs act on multiple pathways at the same time to effectively reduce MIRI, as shown in Figure 1. Therefore, it is highly possible for NPPs to be developed into potent anti-MIRI drugs, with low toxicity. At present, the research on reducing MIRI using NPPs is mainly focused on flavonoids and saponins. The relationship between the chemical structure of NPPs and its anti-MIRI bioactivity remains to be discovered. Understanding of the molecular mechanisms underlying the activities of different types of NPPs against MIRI has gradually deepened; however, most of the studies are limited to animal and cell models, and research into the clinical application of NPPs is limited.
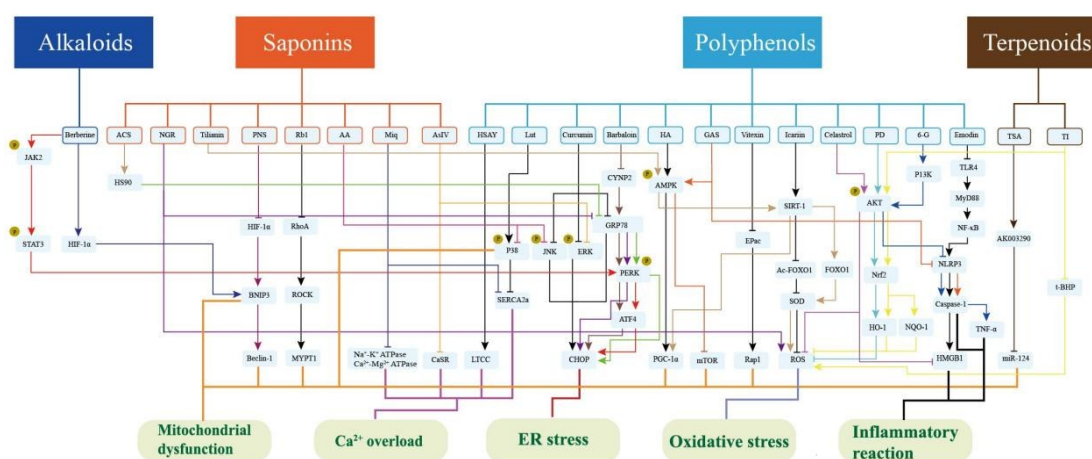
Figure 1. NPPs can inhibit MIRI-induced mitochondrial dysfunction, Ca^{2+} overload, ER stress, oxidative stress and inflammatory reaction by regulating signal pathways.

There are some shortcomings in the safety of NPPs in clinical application, including the following aspects: the mechanism of action of NPPs is complex; the active ingredients are difficult to determine; the dose and frequency of use are difficult to control; it may have poor efficacy or excessive reactions. In addition, the drug utilization of NPPs is generally low, thus larger doses and longer administration cycles are required, and this may cause toxic reactions [175]. There are many interactions and interference factors between NPPs and other therapeutic drugs, which need to be evaluated and controlled in detail, according to the physiological characteristics and conditions of specific patients.

Future research on the use of NPP for treatment of MIRI needs to further explore NPPs' anti-MIRI mechanism and the structure-activity relationship of NPPs. It is necessary and urgent to translate new research into clinical treatment programs.

Conflicts of Interest: The authors declare no conflict of interest.

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