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Review paper

Potential of natural drug modulation of endoplasmic reticulum stress in the treatment of myocardial injury

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ABSTRACT

Myocardial injury (MI) is a common occurrence in clinical practice caused by various factors such as ischemia, hypoxia, infection, metabolic abnormalities, and inflammation. Such damages are characterized by a reduction in myocardial function and cardiomyocyte death that can result in dangerous outcomes such as cardiac failure and arrhythmias. An endoplasmic reticulum stress (ERS)-induced unfolded protein response (UPR) is triggered by several stressors, and its intricate signaling networks are instrumental in both cell survival and death. Cardiac damage frequently triggers ERS in response to different types of injuries and stress. High levels of ERS can exacerbate myocardial damage by inducing necrosis and apoptosis. To target ERS in MI prevention and treatment, current medical research is focused on identifying effective therapy approaches. Traditional Chinese medicine (TCM) is frequently used because of its vast range of applications and low risk of adverse effects. Various studies have demonstrated that active components of Chinese medicines, including polyphenols, saponins, and alkaloids, can reduce myocardial cell death, inflammation, and modify the ERS pathway, thus preventing and mitigating cardiac injury. Thus, this paper aims to provide a new direction and scientific basis for targeting ERS in MI prevention and treatment. We specifically summarize recent research progress on the regulation mechanism of ERS in MI by active ingredients of TCM.

1. Introduction

The endoplasmic reticulum (ER) is a multifunctional organelle that plays a critical role in protein and lipid production, processing, and transport [1]. Apart from synthesizing cellular lipids like glycerophospholipids, ceramides, and cholesterol, it also coordinates protein folding and translocation, transmembrane, and secretion. Additionally, ER controls cellular signaling, storage, and uptake of Ca^{2+} [2]. Endoplasmic reticulum stress (ERS) is the competition of ER homeostasis, causing the accumulation of misfolded and unfolded proteins, brought on by cellular events that are pathologic [3].

Myocardial damage is a crucial component of cardiovascular illnesses diseases (CVDs), the leading cause of death and morbidity globally [4]. Myocardial injury (MI) can develop due to diverse pathological conditions such as hypertension, ischemic heart disease, heart failure, myocardial infarction, metabolic cardiomyopathy, space weightlessness, and heat stress, among others [5–7].

Pathophysiologic factors that contribute to developing cardiovascular diseases, such as inflammation, hypoxia, and metabolic disorder, place substantial demands on the ER protein folding machinery, leading to ERS [8–10]. The non-adaptive unfolded protein response (UPR) triggers apoptosis, leading to ERS and damages cardiomyocytes, while oxidative stress and inflammation become imminent due to ERS, ultimately impacting CVDs [9,11]. Targeting ERS, particularly non-adaptive UPR, has become a practical therapeutic option for managing diseases due to the significant role played by ERS in CVDs' pathophysiology.

Although many drugs can treat CVDs, using existing medications in the long-term results in adverse effects such as rhabdomyolysis, renal failure, and hemorrhage [12]. The invention of novel medications has benefited significantly from natural products derived from plants, animals, and microorganisms, fostering human healthcare [13]. Numerous researches have shown that several natural substances can protect damaged myocardium by targeting ERS pathways. Therefore, natural compounds targeting the ERS pathway are significant as an effective treatment approach to minimize myocardial damage.

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2. Methodology

A comprehensive search of electronic databases such as Scopus, PubMed, Web of Science, and Google Scholar was carried out using specific grid terms, including “ERS”, “ERS and myocardial protection”, “ERS and MI”, and “natural products of myocardial protection”. Moreover, bibliographies of all retrieved publications up to January 2024 were also reviewed for information on *in vivo*, *in vitro*, and human clinical investigations where natural products were employed to target at least one mediator of ERS involved in cardiovascular diseases.

3. ERS

The accumulation of unfolded proteins in the lumen of the ER, caused by nutritional shortages, hypoxia, genetic mutations, infections, disruptions in Ca^{2+} homeostasis, redox imbalance, altered protein glycosylation, and overexpression of folding-deficient proteins, results in ERS [14,15]. ERS is characterized by the buildup of unfolded proteins, and in response, the adaptive mechanism called the UPR is activated to reestablish ER homeostasis [16]. The UPR stimulates two distinct pathways, adaptive and pro-apoptotic. To restore ER homeostasis, four essential pathways are maintained: a) reducing protein production to prevent the further accumulation of unfolded and misfolded proteins, b) transcriptionally activating ER chaperone genes such as glucose regulated protein78 (GRP78)/binding-immunoglobulin protein (BiP) or glucose regulatory protein94 (GRP94) to promote protein folding, c) transcriptionally upregulating ER-associated degradation (ERAD) component genes to increase degradation of unfolded proteins via the ubiquitin-proteasome pathway, and d) initiating apoptosis to eliminate ERS-damaged cells, thereby ensuring survival of the organism [15]. However, in chronic ERS, if the adaptive UPR pathway fails to restore homeostasis, apoptotic pathways such as protein kinase RNA (PKR)-like ER kinase (PERK), calcium signaling, inositol-requiring enzyme 1 (IRE1)-c-Jun N-terminal kinase (JNK)-mediated apoptosis, and C/EBP homologous protein(CHOP)-mediated apoptosis can result in cell death.

3.1. Adaptive pathways of the UPR

Adaptive mechanisms, such as the UPR and ERAD, are enacted to combat high ERS. The UPR is an adaptive response to reduce ERS conditions, which is triggered by protein buildup in the ER lumen during protein misfolding. In contrast, ERAD regulates the ER lumen's capacity to eliminate misfolded proteins [17]. Three separate branches of the UPR, controlled by IRE1, PERK, and activating transcription factor 6 (ATF6), respectively, initiate when ER transmembrane sensors detect the accumulation of unfolded proteins in the ER [18]. The UPR attempts to restore protein deposition, but sustained activation of the UPR results in a maladaptive response [17]. Normally, the ER molecular chaperone GRP78/BiP binds to the luminal structural domain to keep the transmembrane sensors of the UPR's adaptive route inactivated: IRE1, PERK, and ATF6 [19]. However, the unfolded protein binds to GRP78 and dissociates it from the transmembrane sensors to activate them and induce the UPR [20]. When the UPR is active, three signaling pathways (IRE1, PERK, and ATF6) are triggered to promote protein folding and restore ER homeostasis (Fig. 1).

3.1.1. IRE1 pathway

IRE1, an ER transmembrane protein of the UPR, is expressed in intestinal epithelial cells and produces two isoforms: IRE1α and IRE1β, which are identified globally in human beings. Upon dissociation of GRP78, IRE1-activated ribonucleic acid endonuclease splices X-box-binding protein 1 (XBP1) mRNA, which encodes a basic leucine-zipper (b-ZIP) transcription factor. This factor upregulates genes that promote folded proteins, such as protein disulfide isomerase (PDI), and genes necessary for ERAD, such as ER degradation-enhanced-alpha-mannose-like protein (EDEM) [20,21]. ERAD, in association with the cytoplasmic ubiquitin-proteasome system (UPS), decreases the accumulation of unfolded proteins, thus restoring ER homeostasis [22]. Molecular chaperones and folding enzymes form a well-established recognition system of ERAD, which selectively transports unfolded proteins for destruction and guides the precise folding of released proteins [23]. Molecular chaperones facilitate proper protein folding, prevent protein aggregation, and regulate mitochondrial and protein breakdown [24].

3.1.2. ATF6 pathway

ATF6 is a transmembrane protein located on the ER that has two isoforms, namely ATF6α and ATF6β. During chronic ERS, GRP78 dissociates from ATF6 and leads to its activation. S1 and S2 proteases then cleave ATF6, resulting in cytoplasmic fragments of ATF6-α that are subsequently transported to the nucleus. These fragments act as transcription factors that regulate the production of XBP1. Specifically, ATF6α heterodimerizes with XBP1 to promote ERAD of the gene [25,26].

3.1.3. PERK pathway

PERK is another UPR-type ER transmembrane protein [27]. In times of ERS, the binding of GRP78 to the luminal structural domain is disrupted, leading to activation of PERK. As a result, the alpha-subunit of eukaryotic translation initiation factor 2 (eIF2) oligomerizes, causing the phosphorylation of Ser51 [28], which in turn halts eIF2 phosphorylation and decreases protein synthesis, influx into the ER lumen, and ER protein loading. Moreover, to attenuate oxidative stress, active PERK phosphorylates nuclear factor erythroid-2-related factor 2 (NrF2), which regulates the expression of genes that respond to antioxidants, such as heme oxygenase 1 (HO-1) and glutathione S-transferase [29].

3.2. Pro-apoptotic pathway

During chronic ERS, if the adaptive mechanisms of the UPR fail to restore *in vivo* equilibrium, several pro-apoptotic signaling pathways will trigger, leading to cell death due to the malfunction of ER [30]. The UPR apoptotic pathway comprises IRE1-JNK, PERK-CHOP, ATF6-CHOP, and the IP3R1-Ca^{2+} channel, which regulates the inositol 1,4,5-trisphosphate receptor type 1 (IP3R1) and Ca^{2+} levels. Apoptosis ensues if the UPR does not stabilize and control ER, as mediated by CHOP, IRE1/tumor necrosis factor receptor-associated factor 2 (TRAF2), and Ca^{2+}-related signaling pathways [30,31](Fig. 2).

3.2.1. IRE1α and CHOP related apoptosis

Chronic ERS triggers the activation of IRE1α, which then phosphorylates and binds to TRAF2 in cytoplasmic structural regions. This interaction activates apoptotic signaling kinase-1 (ASK1) [32,33]. ASK1, by inactivating the anti-apoptotic BCL2 apoptosis regulator (Bcl-2) protein, activates kinases such as JNK, which stimulate BAK and BAX. These, in turn, release cytochrome C and cause apoptosis via the intrinsic apoptotic pathway [34]. Furthermore, CHOP is an apoptotic marker in ERS, and is often referred to as the growth arrest and DNA damage-inducible gene (GADD153). In severe and irreversible ERS, the PERK-eIF2-activating transcription factor 4 (ATF4)-CHOP pathway is preferred, while all three UPR apoptotic pathways support programmed death in CHOP [35].

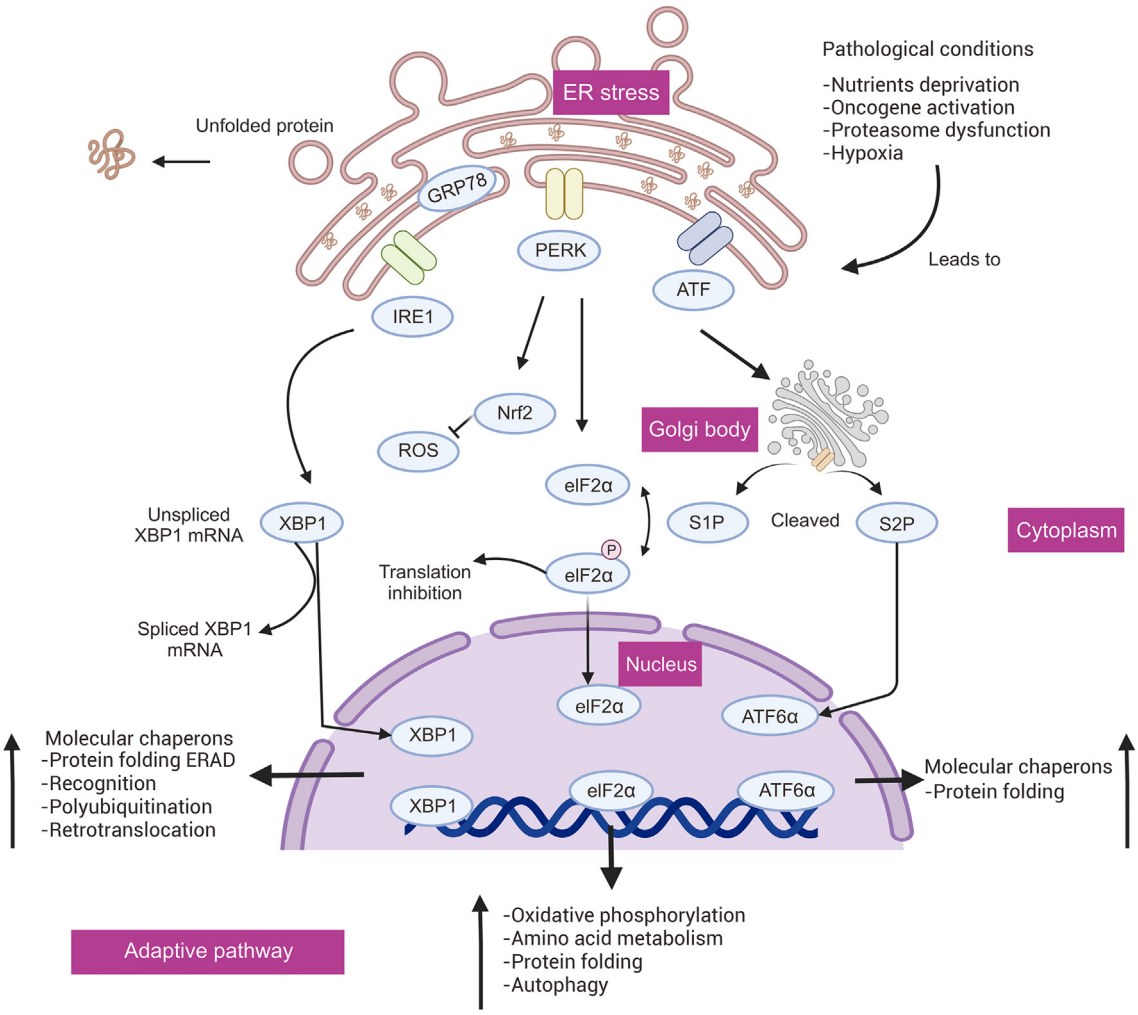

Fig. 1. Endoplasmic reticulum stress (ERS) activates adaptive signaling pathways. ER: endoplasmic reticulum; GRP78: glucose regulated protein78; IRE1: inositol-requiring enzyme 1; PERK: protein kinase RNA (PKR)-like ER kinase; ATF: activating transcription factor; XBP1: X-box-binding protein 1; ROS: reactive oxygen species; Nrf2: nuclear factor erythroid-2-related factor 2; eIF2α: eukaryotic translation initiation factor 2α; S1P: site 1 protease; S2P: site 2 protease; ATF6: activating transcription factor 6; ERAD: ER-associated degradation.

3.2.2. *Calcium signaling apoptotic pathway*

Calcium signaling pathways have been linked to CHOP-mediated apoptosis. Activation of CHOP-dependent ER oxidase 1 alpha promotes calcium release via IP3R1 [36], which in turn activates the calcium-sensing enzyme Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII). This leads to the activation of various downstream apoptotic pathways such as Fas cell surface death receptor (FAS), JNK activation, and mitochondrial apoptogen release [37]. Furthermore, matrix-interacting molecule 1 (Stim1) has a crucial role in ERS through its regulation of the calcium pathway. Stim1 senses Ca^{2+} levels in the ER through its EF-hand structural domain [38] and translocates to the plasma membrane when Ca^{2+} is depleted in the ER. In this state, Stim1 interacts with and activates ORAI1, a subunit of the Ca^{2+} release-activated Ca^{2+} channel (CRAC), which facilitates calcium entry into the cell [39]. Dysfunctional Stim1 directly affects Ca^{2+} levels in the ER, leading to the initiation or exacerbation of ERS. If Stim1 is impaired, it may result in an imbalance of Ca^{2+} homeostasis in mitochondria, thus affecting mitochondrial structure and function [40]. This imbalance leads to cytochrome C release from mitochondria and reduces mitochondrial membrane potential, which ultimately induces mitochondria-driven apoptosis [41].

4. An overview of advances in ERS in MI disease

MI and vascular endothelial damage are typical consequences of a range of prevalent cardiovascular conditions, including hypertension, coronary heart disease, and heart failure, which are all triggered by varied stress stimuli. Preserving homeostasis in the ER is intricately linked to the proper functioning of the cardiovascular system. ERS serves as a contributor to, and a result of, various cardiovascular diseases such as stroke, hypertension, ischemic heart disease, heart failure and different cardiomyopathies (Fig. 3). This cycle of disease has the potential to trap the body [9,11].

4.1. *ERS and ischemic heart disease*

After ischemia/reperfusion (I/R), myocardial infarction is a common cause of MI, characterized by the production of pro-inflammatory cytokines, oxygen and nutrient depletion, and sudden load of oxygen free radicals into the heart, leading to inflammation and myocardial death [42]. The activation of pro-apoptotic pathways and the UPR can respond to these stimuli [43,44]. While pathogenic ERS induces apoptosis, the adaptive UPR can be helpful in myocardial I/R injury. Supporting this, genetically modified mice

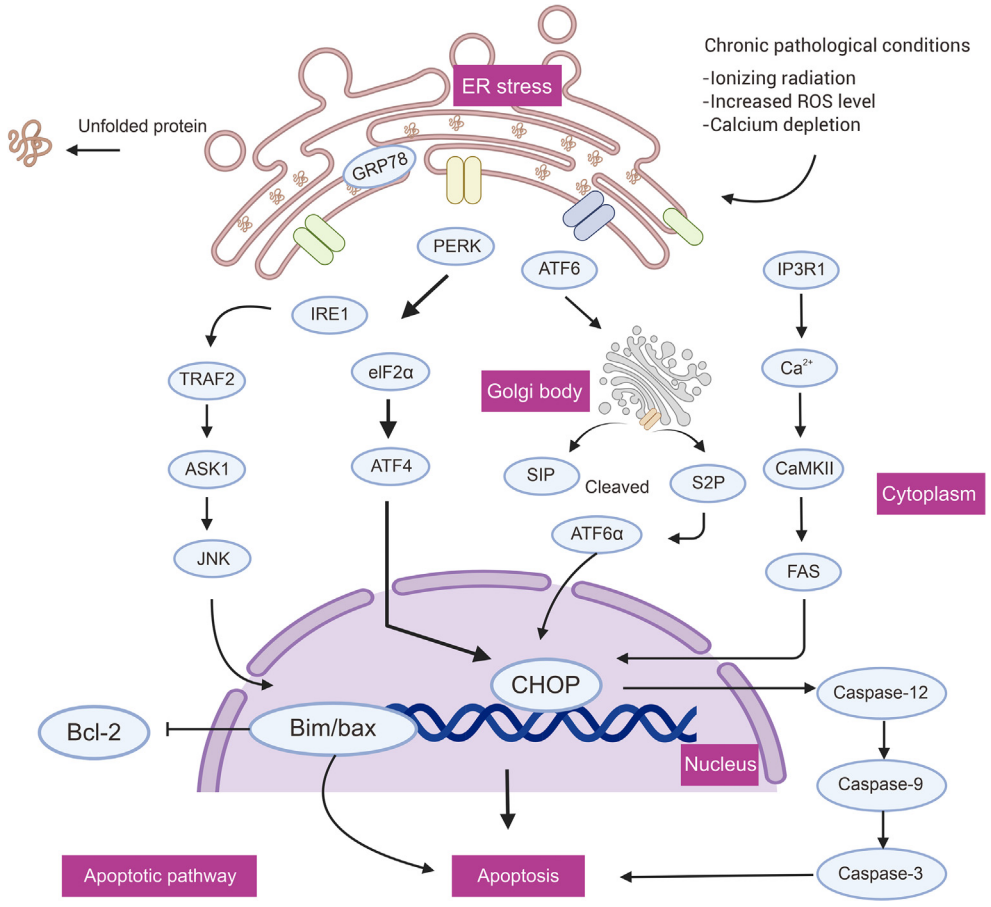

Fig. 2. Endoplasmic reticulum stress (ERS) activates pro-apoptotic signaling pathways. ER: endoplasmic reticulum; GRP78: glucose regulated protein78; IRE1: inositol-requiring enzyme 1; PERK: protein kinase RNA (PKR)-like ER kinase; ATF: activating transcription factor; eIF2α: eukaryotic translation initiation factor 2α; ATF4: activating transcription factor 4; ATF6: activating transcription factor 6; TRAF2: tumor necrosis factor receptor-associated factor 2; ASK1: apoptotic signaling kinase-1; JNK: c-Jun N-terminal kinase; S1P: site 1 protease; S2P: site 2 protease; IP3R1: inositol 1,4,5-trisphosphate receptor type 1; CaMKII: Ca^{2+}/calmodulin-dependent protein kinase II; FAS: Fas cell surface death receptor; CHOP: C/EBP homologous protein; Bcl-2: BCL2 apoptosis regulator.

and pharmacological methods have further shown the advantageous adaptive role of ATF6 in myocardial I/R injury by promoting ERAD and misfolded protein degradation in the ER [45]. In mice with I/R injury, XBP1s is cardioprotective, and XBP1 mRNA splicing takes place and positively regulates ER activity in cardiac I/R injury. Utilizing strategies to activate the UPR may function as endogenous adaptive stress responses to counteract pathologic ERS caused by I/R injury. However, downstream PERK targets, such as CHOP, p53 upregulated apoptosis regulator (PUMA), and tribbles homolog 3 (TRIB3) may induce ERS-induced cell death following myocardial I/R injury. In mice with myocardial I/R injury, PAK2 downregulation precedes ERS, caspase-12 activation, ROS generation, apoptosis, and Ca^{2+} overload. Understanding the distinct functions of UPR elements and ERS in myocardial I/R injury could pave the way for the development of therapeutic intervention techniques.

4.2. ERS and heart failure

An increasing body of literature has indicated that ERS significantly influences heart failure and cardiac remodeling. Various factors, such as hypoxia and acute/chronic inflammatory reactions, can cause ERS in cardiomyocytes [46]. Structural alterations in ER and UPR components in cardiomyocytes have been found in patients with heart failure or cardiac hypertrophy [47,48]. The proliferation of ER tubules, observed during electron microscope examination, is a common characteristic of degenerating cardiomyocytes, indicating an overload of the ER in this state. Nonetheless, the adaptive UPR maintains cardiac homeostasis, whereas excessive ERS and stress-induced apoptosis are primarily due to cardiac pressure overload [49]. Elevated levels of CHOP and caspase-12 in failing human hearts signify an association between UPR activation and the pathogenesis of HF in humans. Likewise, in a model of azithromycin-induced heart failure, increased levels of GRP78 and CHOP were observed [50]. In this regard, apoptosis generated by ERS could be considered as the shared pathophysiological mechanism of heart failure caused by a variety of reasons. Overall, the findings suggest that molecules linked to ERS could be utilized as molecular targets in the treatment of heart failure and hypertrophy.

4.3. ERS and cardiomyopathy

ERS is a variable associated with the pathophysiology of cardiomyopathy [51]. Risk factors such as alcohol consumption, free fatty acid levels, and hyperglycemia can cause ERS, which, in turn, exacerbates the disease [52,53]. Increased levels of BiP, CaMKII, CHOP, mitogen-activated protein kinase (MAPK), and cleaved ATF6 are linked to autoimmune cardiomyopathies resulting in apoptosis, ventricular dilatation, and cardiac failure [54,55]. Furthermore, ERS and non-adaptive UPR contribute to diabetic cardiomyopathy (DCM) by inducing apoptosis via the PERK and ATF6 pathways [56]. Therefore, a supplement of taurine ursodeoxycholic acid (TUDCA) that reduces oxidative stress and encourages cell survival signals has been proposed to improve myocardial metabolism and alleviate

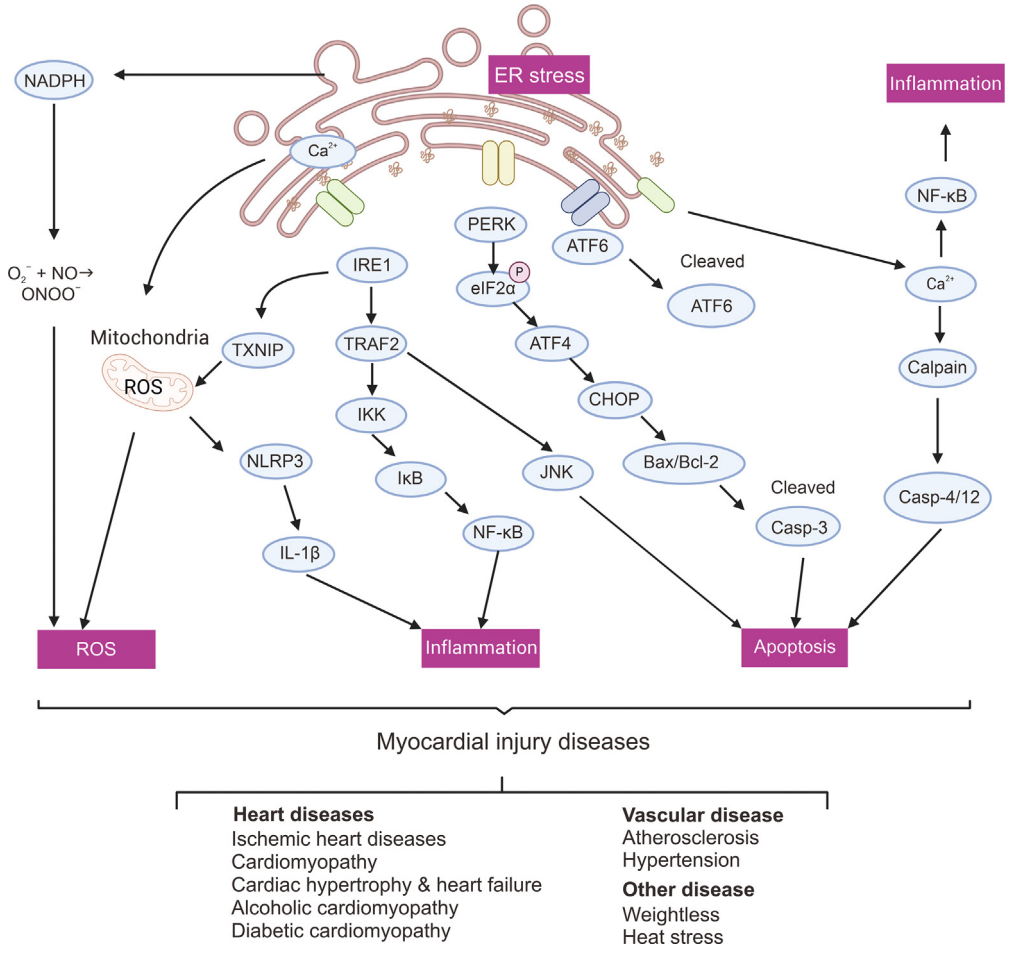

Fig. 3. Endoplasmic reticulum stress (ERS)-induced unfolded protein responses (UPRs) are associated with various signaling pathways in myocardial injury (MI). NADPH: nicotinamide adenine dinucleotide phosphate oxidase; ER: endoplasmic reticulum; ROS: reactive oxygen species; TXNIP: thioredoxin interacting protein; NLRP3: NLR family fyrin domain containing 3; IL-1β: interleukin 1beta; IRE1: inositol-requiring enzyme 1; TRAF2: tumor necrosis factor receptor-associated factor 2; IKK: inhibitor of kappa B kinase; NF-κB: nuclear factor kappa-B; IκB: inhibitor of NF-κB; PERK: protein kinase RNA (PKR)-like ER kinase; eIF2α: eukaryotic translation initiation factor 2α; ATF4: activating transcription factor 4; CHOP: CCAAT/enhancer-binding protein homologous protein; Bcl-2: BCL2 apoptosis regulator; ATF6: activating transcription factor 6.

cardiac injury [57]. On the other hand, ERS signaling pathways (PERK-eukaryotic translation initiation factor 2α (eIF2α)-ATF4, ATF6, and IRE1-XBP1) are activated in ethanol-induced dilated cardiomyopathy leading to apoptosis and altering cardiac mentation and remodeling. The significance of cholesterol metabolism in the development of metabolic cardiomyopathy has been acknowledged in recent years. Sterol regulatory element-binding proteins (SREBPs) have specifically been noted to affect the processing and synthesis of ATF6 [58,59], hence contributing to ERS [60]. Regulating the activity of SREBPs may improve ERS, myocardial metabolism, and blood supply, and attenuate the symptoms of metabolic cardiomyopathy [61].

4.4. ERS and atherosclerosis

Atherosclerosis is a primary pathological basis for numerous CVDs, and a prevalent risk factor for myocardial damage, causing significant impairment in people's quality of life. Multiple atherosclerosis risk factors lead to ERS, including reactive nitrogen generation, oxidative stress, hyperhomocysteinemia, and the accumulation of free cholesterol in macrophages [46,62].

Molecular pathways linked to dysfunctional UPR and ERS have been found to play a role in the development of atherosclerosis. Judging from the elevated levels of the ERS markers BiP and CHOP in human coronary artery lesions, we can conclude that ERS and the ERS response are involved in the development of atherosclerosis and the induction of smooth muscle cell apoptosis [63]. Endothelial cells that suffer from shear stresses promoting atherosclerosis exhibit a marked increase in ERS [64]. Additionally, according to transcriptional profiling, genes linked to ERS were consistently found to be upregulated in the endothelium of all atherosclerosis-prone areas [65].

Dong et al. [66] suggested that by preserving intracellular Ca^{2+} homeostasis and sarcoplasmic reticulum calcium transporting ATPase (SERCA) activity, 5′ adenosine monophosphate-activated protein kinase (AMPK) acts as a physiological inhibitor of ERS, as they found the suppression of endothelial cells' SERCA activity, and a dramatic increase in ERS when AMPK deficiency was present. Atherosclerosis poses a significant threat to public health, causing a high number of morbidity and deaths from CVDs. Therefore, tackling ERS and aberrant UPR might be a promising direction for treating and preventing atherosclerosis.

4.5. ERS and other MI diseases

Various factors that lead to myocardial damage have come to light in addition to prevalent cardiovascular diseases. Heat stress influences heart failure, myocardial damage and cardiac insufficiency [67]. Heat exposure leads to increased ROS levels causing oxidative damage to the heart tissue, while heat shock-driven ERS causes apoptosis. Heat stress-induced cardiac damage triggered

significantly increased levels of cardiomyocyte angiotensin II (Ang II) and heart troponin I (cTn-I), which was linked to higher levels of ERS-related proteins GRP78 and CHOP. As space exploration programs continue, novel health issues have emerged. It has been found that the heart undergoes cardiac remodeling and MI when it's weightless. Ca^{2+} overload and ERS, elevated levels of cardiac trophoblast protein T (cTnT), creatine kinase-MB (CK-MB) in blood, and cardiomyocyte death are some of the consequences of activation of the Erk1/2 and CaMKII/histone deacetylase 4 (HDAC4) signaling pathways in weightless environments. Panax quinquefolium triggers the AMPK pathway, thereby repairing the damaged myocardium and reducing this injury. Furthermore, ERS is linked to numerous cardiovascular disorders and causes significant physiological dysfunction in cardiomyocytes. ERS-related substances may offer novel therapeutic approaches for targeted therapy aimed at alleviating cardiac damage.

5. Natural products targeting ERS for the treatment of MI

Cardiovascular disorders related to myocardial damage have been extensively studied in connection with natural compounds obtained from plants, bacteria, algae, and fungi that target ERS [68]. For this purpose, we summarized the mechanism of action of several active ingredients of Chinese herbal medicines used for the treatment of MI in Table 1 [69–117], and presented in Fig. 4.

5.1. Natural products target ERS mediated MI in I/R injury

5.1.1. Anisodamine

Anisodamine (Fig. 4) is a versatile tropane alkaloid derived from the Chinese herb *Hyoscyamus niger* L. Its unique vascular properties make it an essential compound in pharmacological research. Specifically, Anisodamine positively impacts stress markers in the ER including IRE-1α, CHOP, ATF4, and thioredoxin interacting protein (TXNIP) [118]. By reducing free radical-induced cellular damage, its administration negates the harmful consequences of stress on the body. Tropine alkaloids have also been noted to improve cardiovascular health by preventing cardiac arrest (CA) and resuscitation-induced I/R injury [119]. Similarly, Anisodamine safeguards the rat heart from calcium-mediated damage, as well as resuscitation-induced injury by inhibiting ERS proteins, such as GRP78, CHOP, and cleaved caspase-3 (Fig. 5 and Table 1). This leads to a significant decrease in cardiomyocyte death [69].

5.1.2. Apigenin-7-O-β-d-(-6″-p-coumaroyl)-glucopyranoside (APG)

APG (Fig. 4) is reported as the primary active compound found in *Clematis tangutica* [120]. Research studies have shown that the ERS-mediated apoptotic pathway plays a crucial role in the pathology of cardiac I/R injury [121]. Pre-treatment of primary cardiomyocytes with APG resulted in the activation of the AMPK signaling pathway, significantly inhibiting myocardial I/R-induced ERS, increasing cell viability and reducing apoptosis which ultimately attenuates myocardial injuries and improves cardiac function (Fig. 5 and Table 1). Therefore, APG could be considered as a natural substance with pharmacological pre-treatment activity, which indicates promising new therapeutic approaches for myocardial I/R injury [70].

5.1.3. Araloside C

Araloside C (Fig. 4) is a cardioprotective triterpenoid that is primarily isolated from *Aralia elata* [122]. Through the inhibition of the ERS pathway (PERK/eIF2α/ATF6) via heat shock protein 90 alpha family class A member 1 (HSP90), araloside C has exhibited the ability to enhance cell survival. It achieves this by reducing the expression of ERS pro-apoptotic proteins CHOP and caspase-12, while also hindering lactate dehydrogenase (LDH) leakage (Fig. 5 and Table 1). Overall, araloside C serves to prevent cardiomyocyte apoptosis and alleviate I/R injury in cardiomyocytes [71].

5.1.4. Astragaloside IV

Astragaloside IV (Fig. 4), a saponin obtained from *Radix Astragali*, has been identified for having cardioprotective properties. Specifically, it has been found to effectively reduce the production of ROS by inhibiting the phosphorylation of eIF2α and the expression of pro-apoptotic proteins, such as caspase-3, caspase-9, and CHOP. Consequently, it has demonstrated the ability to prevent apoptosis caused by oxidative stress and ERS. In turn, it has improved the survival rates of H9c2 cells following I/R treatment [72]. The anti-inflammatory and anti-endothelial cell loss effects of Astragaloside IV have also been observed, which are facilitated by the inhibition of TXNIP/NLR family fyrin domain containing 3 (NLRP3) [123] (Fig. 5 and Table 1).

5.1.5. Atractylenolide III

Atractylenolide III (Fig. 4), the principal active component found in *Atractylodes macrocephala Koidz*, has demonstrated beneficial effects in various pharmacological studies, including antioxidant and antiallergic properties [124]. Atractylenolide III is known to exhibit strong binding activity with ERS essential protein GRP78. Consequently, it is able to alleviate ERS, reduce cardiomyocyte apoptosis and protect cardiomyocytes by down-regulating the levels of GRP78, caspase-12 and caspase-3 proteins, and GRP78 and caspase-12 mRNA in hydrogen peroxide-induced H9c2 cardiomyocytes [73] (Fig. 5 and Table 1).

5.1.6. Berberine

Berberine (Fig. 4), an isoquinoline-derived alkaloid, is present in *Rhizoma coptidis*, which has been a crucial component of traditional Chinese medicine (TCM) for over 2,500 years. Its primary use has been to treat dysentery and infectious diarrhea [125]. Berberine effectively suppresses ERS caused by myocardial I/R injury through the down-regulation of the protein kinase RNA-like ER kinase (PERK) and eIF2α phosphorylation, and expression of ATF4 and CHOP in heart tissues. Moreover, Berberine exhibited a reduction in the myocardial infarct size induced by I/R injury, a promotion of cardiac function and a prevention of myocardial apoptosis and oxidative damage during *in vivo* tests performed on rats that underwent I/R surgery [74] (Fig. 5 and Table 1).

5.1.7. Crocin

Crocin, a bioactive compound found in *Crocus sativus* L, has demonstrated numerous pharmacological actions. Studies on crocin have shown that it exerts antioxidant, anti-inflammatory, anticancer, anti-atherosclerotic, and antidepressant effects [126]. Crocin has also been found to reduce cardiomyocyte death rate in animal models and primary cardiomyocytes induced by I/R. By preventing I/R damage, crocin decreases the expression of proteins such as Bax, caspase-3, GRP78, and CHOP while concomitantly enhancing the expression of Bcl-2. These protective effects on cardiomyocytes may be attributed to the regulation of ERS mediated through the miR-34a/silencing information regulator 1(SIRT1)/Nrf2 pathway [75] (Fig. 5 and Table 1).

5.1.8. Elatoside C

Communia araliae is a plant that is distributed extensively in northeast China, eastern Russia, Japan, and Korea [127]. Its roots and bark have been used in TCM as tonic, antiarrhythmic, anti-arthritic, antihypertensive, and antidiabetic agents [128]. Elatoside C (Fig. 4), a major triterpenoid compound that is isolated from aralia, has been demonstrated to inhibit ERS, by inhibiting GRP78,

Table 1
Mechanisms of Chinese herbal medicine active ingredients regulating endoplasmic reticulum stress (ERS).

Active ingredients	Chemical formula	Mechanism and effect	The disease of myocardial injury	Experimental model	Dose	Refs.
Anisodamine	$C_{17}H_{23}NO_4$	↓GRP78, CHOP, Cleaved Caspase-3	Myocardial injury after cardiac arrest and resuscitation in rats	Cardiac and I/R injury and arrest Wistar rats (*in vivo*)	10 mg/kg	[69]
Apigenin-7-O-β-d-(-6″-p-coumaroyl)-glucopyranoside	$C_{30}H_{26}O_{12}$	↓PERK, p-PERK, eIF2α, p-eIF2α, CHOP, Bax, Cleaved Caspase-3, ↑Bcl-2, p-AMPK, AMPK,	Myocardial hypoxia-reperfusion injury	Myocardial ischemia/reperfusion injury isolated heart of adult SD rats (*in vivo*) Hypoxia/Reoxygenation injury in primary neonatal rat cardiomyocytes (*in vitro*)	4 μM	[70]
Araloside C	$C_{53}H_{84}O_{23}$	↓PERK, eIF2α, ATF6, CHOP, Caspase-12, ↑HSP90	Myocardial hypoxia-reperfusion injury	Hypoxia/Reoxygenation injury in H9c2 cardiomyocytes	12.5 μM	[71]
Astragaloside IV	$C_{41}H_{68}O_{14}$	↓p-eIF2α, CHOP, Caspase-3, Caspase-9, ROS, ↑Bcl-2	Myocardial hypoxia-reperfusion injury	Hypoxia/Reoxygenation injury in H9c2 cardiomyocytes (*in vitro*)	50, 10, 5, 1 and 0.5 μM	[72]
Atractylenolide III	$C_{15}H_{20}O_3$	↓GRP78, Caspase-12, Caspase-3, Ca^{2+}	Myocardial hypoxia-reperfusion injury	Hypoxia/Reoxygenation injury in H9c2 cardiomyocytes (*in vitro*)	15, 30 and 60 μM	[73]
Berberine	$C_{20}H_{18}NO_4]+$	↓ PERK, eIF2α, ATF4, CHOP	Myocardial hypoxia-reperfusion injury	Myocardial I/R injured in SD rats (*in vivo*) Hypoxia/Reoxygenation injury in H9c2 cardiomyocytes (*in vitro*)	200 mg/kg/d for 2 week; 50 μM	[74]
Crocin	$C_{44}H_{64}O_{24}$	↓GRP78, Caspase 3, Bax, miR-34a, ↑SIRT1, Nrf2, HO-1	Myocardial hypoxia-reperfusion injury	I/R-induced left ventricular dysfunction and infarct in C57BL/6 mice (*in vivo*) Hypoxia/Reoxygenation injury in primary neonatal mouse cardiomyocytes (*in vitro*)	50 mg/kg/d for 1 week; 10 μM	[75]
Elatoside C	$C_{46}H_{74}O_{16}$	↓GRP78, CHOP, Caspase-12, JNK	Myocardial hypoxia-reperfusion injury	Hypoxia/Reoxygenation injury in H9c2 cardiomyocytes (*in vitro*)	25 μM	[76]
Grape seed proanthocyanidins	$C_{30}H_{26}O_{13}$	↓GRP78, CHOP, eIF2α, p-PERK	Myocardial hypoxia-reperfusion injury	Hypoxia/Reoxygenation injury in H9c2 cardiomyocytes (*in vitro*)	50, 100 and 200 μM	[77]
Gypenoside	$C_{47}H_{80}O_{17}$	↓CHOP, GRP78, CHOP, Caspase-12, PERK, eIF2α, ATF4 ↑PI3K, Akt, p-GSK3β	Myocardial hypoxia-reperfusion injury; coronary heart diseases	Myocardial I/R injured in Wistar rats (*in vivo*) Hypoxia/Reoxygenation injury in H9c2 cardiomyocytes (*in vitro*)	200 mg/kg for 1 week	[78]
Gypenoside XVII	$C_{48}H_{82}O_{18}$	↓GRP78, PERK, IRE1, P-JNK, CHOP, Bad, BAX, Caspase-12, p38-MAPK pathway ↑Bcl-2, PI3K/Akt pathway	Myocardial hypoxia-reperfusion injury	Hypoxia/Reoxygenation injury in H9c2 cardiomyocytes (*in vitro*)	5, 10 and 20 μM	[79]
Luteolin	$C_{15}H_{10}O_6$	↓GRP78, p-eIF2α, IRE1α, XBP-1, ATF6, CHOP, Bax, Caspase-3, ↑Bcl-2	Myocardial hypoxia-reperfusion injury	Hypoxia/Reoxygenation injury in H9c2 cardiomyocytes (*in vitro*)	10 μM	[80]
Lycopene	$C_{40}H_{56}$	↓CHOP, GRP78, ATF6, eIF2α, sXBP-1, Bax/Bcl-2,	Myocardial hypoxia-reperfusion injury	Hypoxia/Reoxygenation injury in primary neonatal rat cardiomyocytes (*in vitro*)	5 μM	[81]
Notoginsenoside R1	$C_{47}H_{80}O_{18}$	↓Calnexin, BiP, CHOP, Caspase-3, ↑RyR2	Myocardial hypoxia-reperfusion injury	Hypoxia/Reoxygenation injury in H9c2 cardiomyocytes, HL-1 cells, and primary cultured neonatal cardiomyocytes from Sprague−Dawley rats (*in vitro*)	20, 40, 80 and 100μg/mL	[82]
Panax quinquefolium saponin	–	↓GRP78, Calreticulin, CHOP, Bax, ↑Bcl-2	Myocardial infarction	Acute myocardial infarction in SD rats (*in vivo*)	50 and 100 mg/kg for 4 week	[83]
Piperine	$C_{17}H_{19}NO_3$	↓GRP78, CHOP, Caspase-12, BiP, ↑p-PI3K, p-AKT	Myocardial ischemia/reperfusion injury	Hypoxia/Reoxygenation injury in primary neonatal rat cardiomyocytes from Sprague-Dawley (*in vitro*)	20 μM	[84]
Protocatechualdehyde	$C_7H_6O_3$	↓eIF2α, p-eIF2α, Ero1-Lα, PERK, CHOP, BiP, IRE1α, ATF6, Caspase-3, BAX, HIF-1α, ↑Bcl-2	Myocardial ischemia/reperfusion injury	Oxygen-glucose deprivation/reoxygenation in H9c2 cardiomyocytes, and primary neonatal rat cardiomyocytes from Sprague Dawley (*in vitro*)	5 μM	[85]
Quercetin	$C_{15}H_{10}O_7$	↓PERK, CHOP, Caspase-12, ↑SIRT1, TMBIM6	Myocardial ischemia/reperfusion injury	Hypoxia/reoxygenation in H9c2 cardiomyocytes (*in vitro*)	150 mg/L	[86]

(*continued on next page*)

Table 1 (*continued*)

Active ingredients	Chemical formula	Mechanism and effect	The disease of myocardial injury	Experimental model	Dose	Refs.
Salidroside	$C_{14}H_{20}O_7$	↓p-PERK, p-eIF2α, CHOP, p-PERK, ↑AMPK	Myocardial ischemia/reperfusion injury	Myocardial ischemia in SD rats (*in vivo*) I/R injury in H9c2 cardiomyocytes (*in vitro*)	40 mg/kg; 10 μM	[87]
Sulforaphane	$C_6H_{11}NOS_2$	↓GRP78, CHOP, caspase-12, SIRT1, PERK, eIF2α, ↑Bcl-2	Myocardial ischemia/reperfusion injury	Ischemia/reperfusion injury in H9c2 cardiomyocytes (*in vitro*)	0.1−5 μM	[89]
Tanshinone IIA	$C_{19}H_{18}O_3$	↓GRP78, CHOP, Caspase-12, ↑miR-133	Myocardial injury	Tunicamycinc induced injury in primary neonatal rat cardiomyocytes (*in vitro*)	10 μM	[90]
Tournefolic acid B	$C_{17}H_{12}O_6$	↓CHOP, Caspase-12, JNK↑SOD、CAT, GSH-Px, p-PI3K, p-AKT, Bcl-2/Bax ratio	Myocardial ischemia/reperfusion injury	Hypoxia/reoxygenation injury in H9c2 cardiomyocytes (*in vitro*)	0.5, 1 and 2 μM	[91]
Baicalin	$C_{21}H_{18}O_{11}$	↓CHOP, ↑eNOS, NO	Clotrimazole-induced apoptosis in cardiomyocytes	Hypoxia/Reoxygenation injury in primary neonatal rat cardiomyocytes from SD rats (*in vitro*)	12.5, 25 and 50 μM	[92]
Barbaloin	$C_{21}H_{22}O_9$	↓GRP78, CHOP, PERK, p-PERK, ATF4, Caspase-12, Caspase-3, CNPY2		Myocardial I/R injured in SD rats (*in vivo*)	20 mg/kg/d for 1 week	[93]
Berberine	$C_{20}H_{18}NO_4$	↓CHOP, Caspase-12, Caspase-3 ↑Bcl-2/Bax ratio	Cardiac remodeling of heart failure after myocardial infarction	Myocardial infarction in Wistar rats (*in vivo*)	20 mg/kg for 4 week	[94]
Echinacoside	$C_{35}H_{46}O_{20}$	↓GRP78, P−I/REα, p-PERK, ATF6, CHOP, NADPH, ROS	Heart failure	Isoprenaline (ISO)-induced HF rats (*in vivo*) Isoprenaline (ISO)-induced primary cardiomyocytes of neonatal from Sprague−Dawley rats (*in vitro*)	10 mg/kg/d for 2 week	[95]
Ophiopogonin D	$C_{44}H_{70}O_{16}$	↓Bip, Bax, Perk、ATF4, Caspase-12, CHOP	Heart failure	Isoprenaline (ISO)-induced cardiac hypertrophy injury in H9c2 cardiomyocytes (*in vitro*)	10 μM	[96]
Resveratrol	$C_{14}H_{12}O_3$	↓GRP78, GRP94, CHOP, ↑Bcl-2/Bax ratio	Cardiac hypertrophy	Isoprenaline (ISO)-induced cardiac hypertrophy injury in H9c2 cardiomyocytes (*in vitro*)	50 μM	[97]
1, 8-cineole	$C_{10}H_{18}O$	↓GRP78, PERK, ATF4, CHOP, ROS, Bcl-2/Bax ratio, p-Caspase 3	Heart failure	Isoprenaline (ISO)-induced cardiac hypertrophy injury in H9c2 cardiomyocytes (*in vitro*)	10, 15, 20, 25, 30, 35 and 40 μM; 120, 60 and 30 mg/kg/d for 4 week	[98]
Astragalus polysaccharides	$C_{10}H_7C_lN_2O_2S$	↓ATF6, PERK, CHOP	Diabetic cardiomyopathy	Streptozotocin-induced type 1 diabetic ratsl (*in vivo*) High Glucose (HG)-Induced H9c2 cardiomyocytes (*in vitro*)	1 g/kg/d for 16 week; 0.8 mg/mL	[99]
Beta carotene	$C_{40}H_{56}$	↓ROS, Bax, ATF4, GRP78, CHOP, Beclin 1, p62, LC3II/LC3I ratio, ↑Bcl-2, p-PI3K, p-AKT, p-mTOR, SOD, GSH-Px	Diabetic cardiomyopathy	Advanced glycation end products-induced H9c2 cardiomyocytes (*in vitro*)	40 μM	[100]
Berberine	$C_{20}H_{18}NO_4]+$	↓XBP1, ↑AMPK, p-eNOS	Diabetes-Associated Endothelial Dysfunction	High-fat diet and streptozotocin induced diabetes in C57BL/6 J mice (*in vivo*) High sugar or clindamycin-treated HUVECs cell (*in vitro*)	11.3, 14.5, 12.2 and 1 μM	[101]
Curcumin	$C_{21}H_{20}O_6$	↓GRP78, CHOP, Caspase 3, BAX,	Diabetic cardiomyopathy	Palmitate treated H9c2 cardiomyocytes (*in vitro*)	10 μM	[102].
Curcumin	$C_{21}H_{20}O_6$	↓p-PERK, p-eIF2α, and ATF4, ↑LC3-II	Lipotoxic cardiomyopathy	Palmitate treated H9c2 cardiomyocytes (*in vitro*)	100 μM	[103]
Linderalactone	$C_{15}H_{16}O_3$	↓ATF6, p-ERK, p-JNK, p38, CHOP, MAPKs	Diabetic cardiomyopathy	Streptozotocin-induced type 1 diabetes in C57BL/6 J mice (*in vivo*)	2.5 or 5 mg/kg for 5 week	[104]
Mangiferin	$C_{19}H_{18}O_{11}$	↓GRP78, CHOP, TXNIP, NLRP3, Caspase-3,↑AMPK, NO	Endothelial dysfunction induced by diabetes	High sugar treated EA.hy926 cells (*in vitro*)	10 μM	[105]
Resveratrol	$C_{14}H_{12}O_3$	↓PERK, eIF2α, ATF6, CHOP, IRE1α, JNK, ↑SIRT1	Diabetic cardiomyopathy	Streptozotocin-induced diabetes in Sprague−Dawley rats (*in vivo*) High sugar treated H9c2 cardiomyocytes (*in vitro*)	10 μM	[106]

Tanshinone IIA	$C_{19}H_{18}O_3$	↓GRP78, ATF4, ATF6, XBP-1s, P-eIF2α, CHOP, ↑SIRT1,	Diabetic cardiomyopathy	High-sugar, high-fat diet induces diabetes in C57BL/6 J mice (*in vivo*) High sugar treated primary neonatal rat cardiomyocytes from C57BL/6 J mouse (*in vitro*)	10, 50 and 250 mg/kg/day for 14 week; 1.5 and 6.25 μM	[107]
Black tea	–	↓ATF3, ATF6, p-eIF2α, ROS	Hypertension-associated endothelial dysfunction	Angiotensin II (Ang II)-induced hypertension in Sprague−Dawley rats (*in vivo*)	15 mg/kg/day for 2 week	[108]
Berberine	$C_{20}H_{18}NO_4]+$	↓AFT3, ATF4, XBP1, COX2, ROS, ↑AMPK	Spontaneously hypertensive	carotid artery tissue of Spontaneously hypertensive rats (*in vivo*)	1 μM	[109]
Nobiletin	$C_{21}H_{22}O_8$	↓GRP78, GRP94, CHOP, Caspase-3	Renal vascular hypertension and left ventricular remodeling	Renal vascular hypertensive Wistar rats (*in vivo*)	100 mg/kg/d for 4 week	[110]
Paeonol	$C_9H_{10}O_3$	↓GRP78, ATF6, eIF2α, ROS, ↑AMPK, PPARδ, NO	Atherosclerosis	Tunicamycin induced C57BJ/6 J and PPARδ wild type (WT) mouse aortas (*in vivo*) Tunicamycin-induced human umbilical vein endothelial cells, H5V cells (*in vitro*)	0.1 μM	[111]
Pterostilbene	$C_{16}H_{16}O_3$	↓PERK, eIF2α, ATF4, CHOP, ↑SIRT1	Atherosclerosis	TNF-α- induced H9c2 cells (*in vitro*)	0.1, 0.5, or 1 μM	[112]
Curcumin	$C_{21}H_{20}O_6$	↓GRP78, CHOP, cTn-I, Ang II, ↑Bcl-2	Heat-stress-induced cardiac injury	Heat stress exposure C57BL/6 J mice (*in vivo*)	50, 100 and 200 mg/kg/day for 4 week	[113]
Rosa canina L, methanolic extract	–	↓p-PERK, p-eIF2α, CHOP, Caspase 8	Heat-stress-induced cardiac injury	Heat stress exposure Wistar rats (*in vivo*)	500/1000 mg/mL	[114]
Ursolic acid	$C_{30}H_{48}O_3$	↓p-PERK, p-eIF2α, CHOP, ↑Mcl-1	Heat stress	Heat stress exposure ICR rats (*in vivo*)	20 or 40 mg/kg	[115]
Panax quinquefolium saponin	–	↓Erk1/2, CaMKII, HDAC4, CK-MB, cTnT, IMA, ↑AMPK	Cardiac remodeling induced by simulated microgravity	Unloading induced cardiac remodeling SD rats (*in vivo*)	200 mg/kg/d for 8 week	[116]
Astaxanthin	$C_{40}H_{52}O_4$	↓GRP78, p-PERK, p-eIF2α, ATF4, ATF6, p-IRE1, XBP-1, CHOP, Caspase-12	Alcoholic cardiomyopathy	Ethanol induced Alcoholic cardiomyopathy in C57BL/6 J mice (*in vivo*) Ethanol treated H9c2 cardiomyocytes and primary cardiomyocytes (*in vitro*)	20 mg/kg/d for 8 week; 10 μM	[117]

GRP78: glucose regulated protein78; CHOP: C/EBP homologous protein; I/R: ischemia/reperfusion; PERK: protein kinase RNA (PKR)-like endoplasmic reticulum (ER) kinase; eIF2α: eukaryotic translation initiation factor 2α; Bcl-2: BCL2 apoptosis regulator; AMPK: 5′ adenosine monophosphate-activated protein kinase; SD rats: Sprague-Dawley rats; ATF6: activating transcription factor 6; HSP90: heat shock protein 90 alpha family class A member 1; ROS: reactive oxygen species; ATF: activating transcription factor; SIRT1: silencing information regulator 1; Nrf2: nuclear factor erythroid-2-related factor 2; HO-1: heme oxygenase 1; JNK: c-Jun N-terminal kinase; RyR2: type 2 ranibodin receptor; Bip: binding-immunoglobulin protein; HIF-1α: hypoxia inducible factor 1 subunit alpha; TMBIM6: transmembrane BAX inhibitor-1 motif-containing 6; CNPY2: cardiomyocyte-specific protein canopy homolog 2; NADPH: nicotinamide adenine dinucleotide phosphate oxidase; LC3II: microtubule associated protein 1 light chain 3 beta; XBP1: X-box-binding protein 1; MAPK: mitogen-activated protein kinase; TXNIP: thioredoxin interacting protein; NLRP3: NLR family fyrin domain containing 3; eNOS: endothelial-type nitric oxide synthase; HUVECs: human umbilical vein endothelial cells; NO: nitric oxide; ATF3: activating transcription factor 3; COX2: cyclooxygenase-2; PPARδ: peroxisome proliferator activated receptor gamma; cTn-I: cardiac troponin I; TNF-α: tumor necrosis factor-α; Ang II: angiotensin II; Mcl-1: MCL1 apoptosis regulator, BCL2 family member; GRP94: glucose regulatory protein94; HDAC4: histone deacetylase 4; CK-MB: creatine kinase-MB; cTnT: cardiac trophoblast protein T; CaMKII: Ca^{2+}/calmodulin-dependent protein kinase II; IMA: ischemia-modified albumin; –: no data.

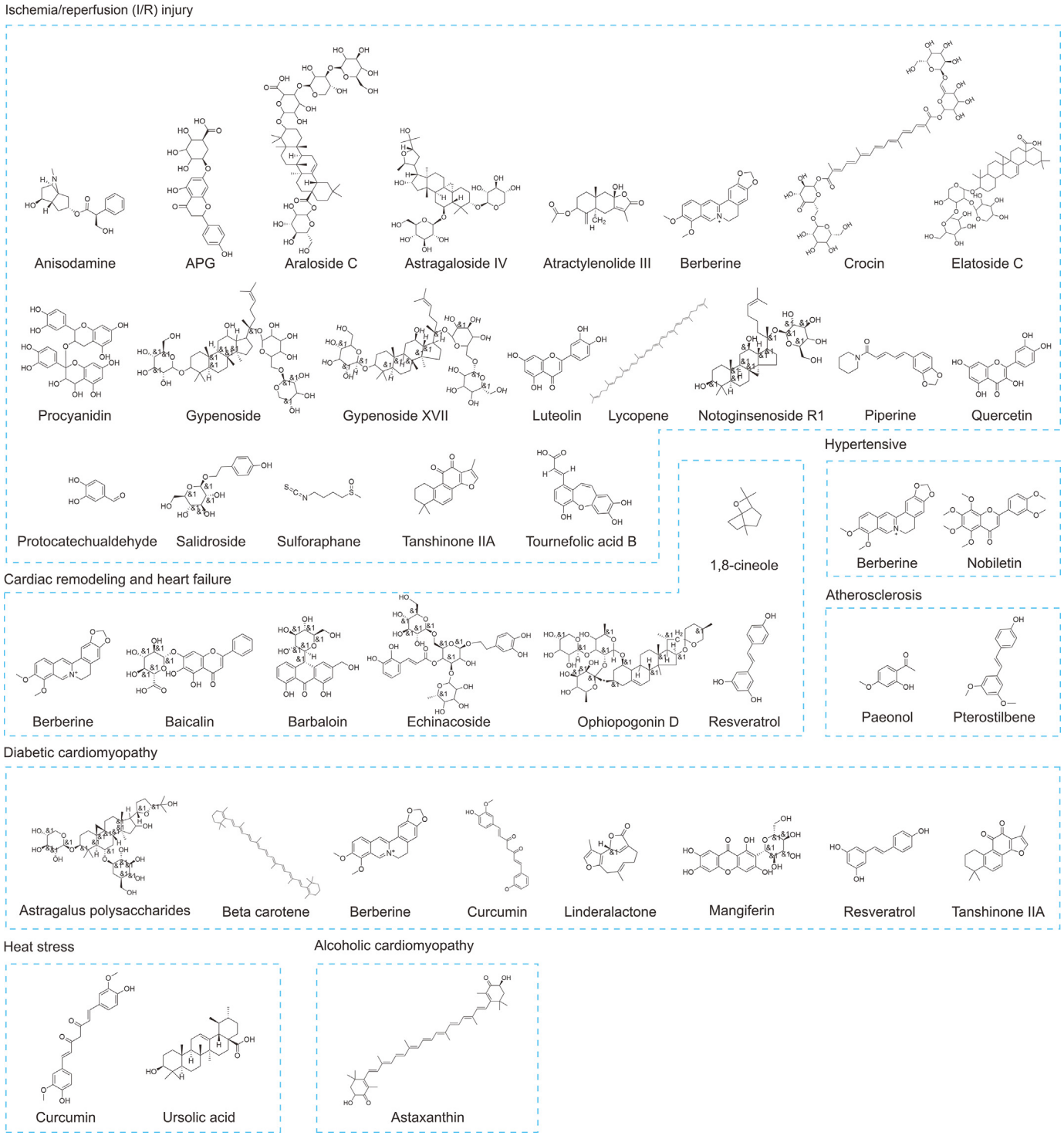

Fig. 4. Molecular structure of natural products targeting endoplasmic reticulum stress (ERS) for treatment of myocardial injury (MI). APG: apigenin-7-O-β-d-(-6″-p-coumaroyl)-glucopyranoside.

CHOP, JNK, and caspase-12, in I/R-induced cardiomyocyte apoptosis. Consequently, this improves mitochondrial membrane potential, cell viability, increases the Bcl-2/Bax ratio and reduces mitochondrial ROS. Therefore, elatoside C might represent an effective therapeutic strategy for mitigating myocardial I/R injury [76] (Fig. 5 and Table 1).

5.1.9. Grape seed proanthocyanidins (GSPs)

Proanthocyanidins are a family of polyphenolic flavonoid compounds found in vegetables and fruits. These compounds contain dimers, trimers, and other oligomers of catechins, epicatechins, and manatee esters. GSPs (Fig. 4) are highly effective antioxidants that can scavenge free radicals as well as vitamin C, E, or beta-carotene

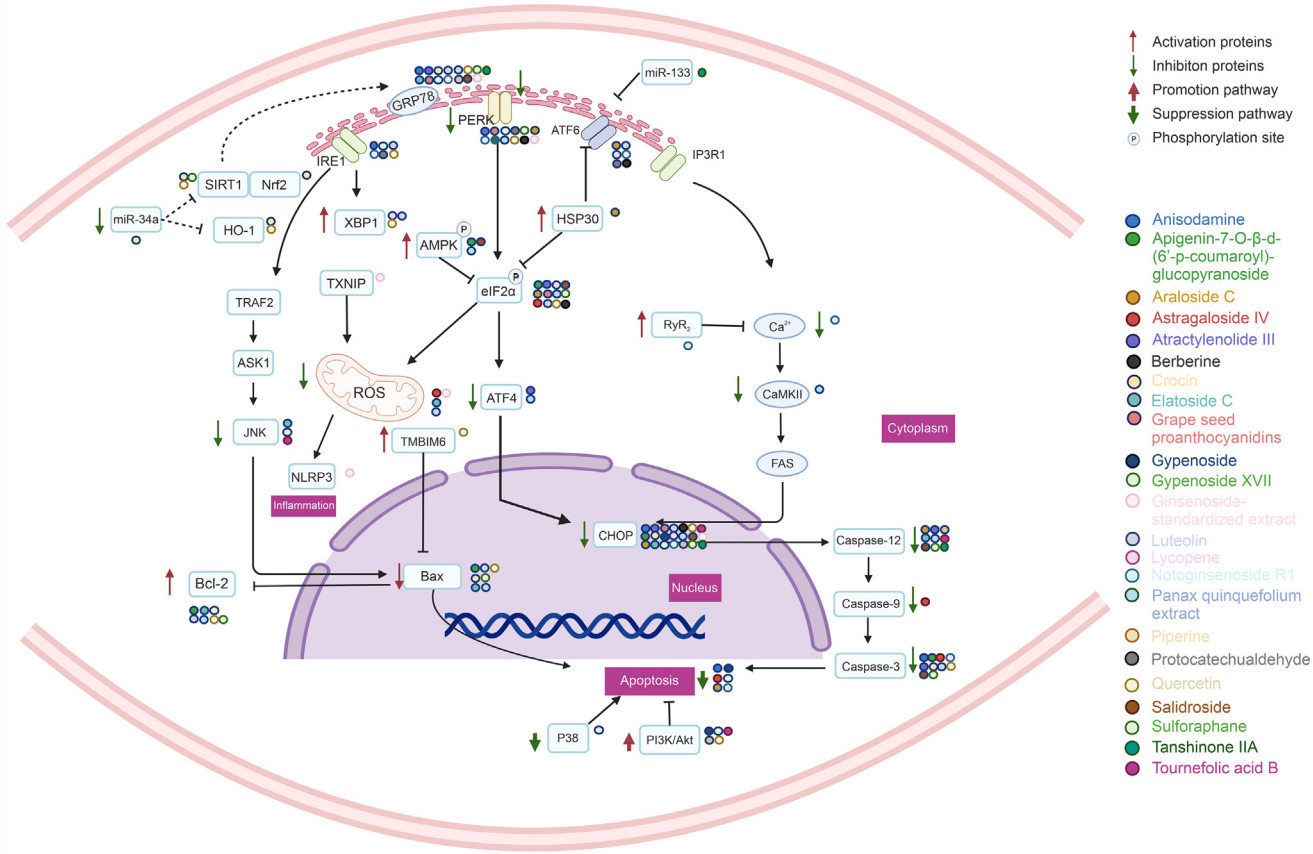

Fig. 5. Natural products target endoplasmic reticulum stress (ERS) mediated myocardial injury (MI) in ischemia/reperfusion (I/R) injury. SIRT1: silencing information regulator 1; Nrf2: nuclear factor erythroid-2-related factor 2; HO-1: heme oxygenase 1; TRAF2: tumor necrosis factor receptor-associated factor 2; ASK1: apoptotic signaling kinase-1; JNK: c-Jun N-terminal kinase; Bcl-2: BCL2 apoptosis regulator; IRE1: inositol-requiring enzyme 1; XBP1: X-box-binding protein 1; TXNIP: thioredoxin interacting protein; ROS: reactive oxygen species; SOD: superoxide dismutase; CAT: catalase; GSH: glutathione; NLRP3: NLR family fyrin domain containing 3; TMBIM6: transmembrane BAX inhibitor-1 motif-containing 6; PERK: protein kinase RNA (PKR)-like endoplasmic reticulum (ER) kinase; AMPK: 5′ adenosine monophosphate-activated protein kinase; eIF2α: eukaryotic translation initiation factor 2α; ATF: activating transcription factor; HSP30: heat shock proteins30; RyR2: ryanodine receptor 2; CaMKII: Ca^{2+}/calmodulin-dependent protein kinase II; CHOP: CCAAT/enhancer-binding protein homologous protein; p38: p38 mitogen-activated protein (MAP) kinase.

[129]. The therapeutic effects of GSPs vary depending on the dosage, with 100 μM demonstrating a cardioprotective effect in H9c2 cardiomyocytes subjected to I/R injury. The use of this dosage reduced the expression of apoptosis-related proteins such as GRP78, CHOP, eIF2α, and p-PERK (Fig. 5 and Table 1), thereby minimizing cardiomyocyte apoptosis and protecting H9c2 cardiomyocytes from I/R injury [77].

5.1.10. Gypenoside

Gynostemma pentaphyllum is an herb commonly used in folk medicine and consumed as herbal tea in various Asian countries. Among its bioactive compounds, gypenoside (Fig. 4) has been identified as the most potent in terms of its anti-inflammatory and antioxidative properties. Studies have shown that gypenoside plays a significant role in protecting against I/R injury in coronary heart disease by reducing oxidative stress. Specifically, gypenoside has been found to inhibit expression of ERS-related proteins and reduce cardiomyocyte apoptosis through blocking the CHOP pro-apoptotic pathway and activating the PI3K/Akt pathway (Fig. 5 and Table 1), thereby ameliorating structural cardiac damage caused by I/R injury [78].

5.1.11. Gypenoside XVII

Gypenoside XVII (Fig. 4), a compound derived from *Panax notoginseng* [130], was found to inhibit myocardial apoptosis and reduce cardiac insufficiency in H9c2 cardiomyocytes. This effect was attributed to the activation of the PI3K/Atk signaling pathway by gypenoside XVII, which delayed the onset of ERS, and to the inhibition of the p38 signaling pathway. Gypenoside XVII significantly suppressed the up-regulation of pro-apoptotic and ERS-associated proteins, namely GRP78, PERK, IRE1, p-JNK, and CHOP (Fig. 5 and Table 1). Moreover, it upregulated the expression of Bcl-2, an anti-apoptotic protein, which contributed to delaying the onset of apoptosis and protecting injured cardiomyocytes [79].

5.1.12. Luteolin

Luteolin (Fig. 4) is a flavonoid found in plants like honeysuckle and foods like carrots, peppers, and celery. Apart from possessing anti-inflammatory properties, it also has endothelial-improving qualities. When tested on the myocardial I/R cell model, several flavonoid interventions, including luteolin, quercetin, rutin, soybean sapogenins, and lignans, significantly improved the survival of cardiomyocytes. This improvement is attributed to the modulation of ERS signature proteins, as well as the expression of various pro- and anti-apoptotic proteins like CHOP, Bcl-2, Bax, and caspase-3 (Fig. 5 and Table 1). Overall, such interventions can attenuate the rate of apoptosis and ameliorate MI [80].

5.1.13. Lycopene

Lycopene (Fig. 4), a member of the carotenoid family, is primarily present in red fruits like tomatoes. Research in epidemiology indicates an inverse association between lycopene levels in serum

and the risk of sudden cardiac death or acute myocardial infarction [131]. In primary mouse cardiomyocytes treated with hypoxia/reoxygenation, lycopene demonstrated a reduction in apoptotic cardiomyocytes and a decrease in the expression of several pro-apoptotic proteins such as CHOP, GRP78, ATF6, eIF2α, and sXBP-1 (Fig. 5 and Table 1). This suggests lycopene could impede cardiomyocyte apoptosis induced by I/R by suppressing ERS and decreasing reactive oxygen species (ROS) [81].

5.1.14. Notoginsenoside R1

Notoginsenoside R1 (Fig. 4), which is a saponin derived from *Panax notoginseng*, has been shown to mitigate ERS by inhibiting oxidative stress pathway and altering the course of I/R damage. Specifically, intervention with notoginsenoside R1 can delay the development of ERS in H9c2 cells by reducing the expression of ERS response proteins including GRP78, p-PERK, ATF6, and IRE1 [43]. Moreover, this compound has been found to scavenge free radicals and elevate the activity of antioxidant enzymes, thus promoting cardioprotective activity and preventing cell death in response to I/R-induced cellular injury [132]. Furthermore, notoginsenoside R1 exerts its effect by downregulating the expression of calcium-linked proteins, BiP, CHOP, and caspase-3 by modulating ryanodine receptor 2 (RyR2)-mediated ER calcium release (Fig. 5 and Table 1), thereby reducing ERS-induced cardiomyocyte injury and apoptosis [82].

5.1.15. Panax quinquefolium extract

Panax Quinquefolium is a species of plant belonging to the family Pentaphyllaceae. American ginseng stem and leaf extracts have been studied for their chemical composition and health benefits for many years. The extracts contain various constituents such as saponins, amino acids, carbohydrates, volatile oils, inorganic elements, and fatty acids which contribute to its benefits to the metabolism [133]. *Panax Quinquefolium* has been found to have potential positive effects on the cardiovascular system. Treatment with Panax Quinquefolium can prevent excessive ERS-associated apoptosis which has a cardioprotective effect in ventricular remodeling following acute myocardial infarction. The treatment can also enhance the expression of Bcl-2 protein while considerably lowering the expression of GRP78, CHOP, and Bax proteins. In rats, treatment with Panax Quinquefolium also resulted in decreased ERS, reduced left ventricular dilation, reduced infarct size, as well as enhanced left ventricular ejection percentage and shortening fraction [83]. Panax Quinquefolium can further block endoplasmic stress-mediated cardiomyocyte apoptosis through the PERK-eIF2α-ATF4-CHOP pathway during I/R and myocardial infarction-induced cardiomyocyte apoptosis [134]. Additionally, Panax Quinquefolium can prevent cell death caused by ERS in cardiomyocytes by decreasing caspase-12 activation levels and the expression of GRP78 and CHOP proteins [84] (Fig. 5 and Table 1).

5.1.16. Piperine

Piperine (Fig. 4) possesses various pharmacological effects, and one that has attracted attention is its capacity to inhibit ERS-induced apoptosis. Myocardial I/R damaged cells displayed elevated apoptosis, along with an increase in the expression of pro-apoptotic proteins such as BiP, CHOP, GRP78, and caspase-12. However, the pretreatment of cardiomyocytes with piperine reversed this trend. This suggests that piperine may have the ability to impede apoptosis onset by adjusting ERS. Furthermore, piperine caused a shift in the expression of PI3K and Akt, which were suppressed before. Through the PI3K/Akt signaling pathway (Fig. 5 and Table 1), piperine manifests its cardioprotective effects, primarily by diminishing ERS-induced apoptosis [84].

5.1.17. Protocatechualdehyde

Protocatechualdehyde (Fig. 4), a natural phenolic compound found in Salvia miltiorrhiza Bunge, has been shown to provide protective effects to cardiomyocytes [135]. In particular, protocatechualdehyde demonstrates anti-apoptotic properties in H9c2 cells exposed to oxygen-glucose deprivation and reoxygenation (OGD/R). Using bioinformatics and experimental studies, it has been revealed that protocatechualdehyde primarily acts by inhibiting the PERK/IRE1α/ATF6α signaling pathway (Fig. 5 and Table 1), leading to the prevention of cardiomyocyte apoptosis mediated by ERS [85].

5.1.18. Quercetin

Quercetin (Fig. 4), a flavonoid naturally found in high concentrations in fruits and vegetables, is known for its antioxidant properties. Quercetin has been shown to restore ER homeostasis in a model of ERS-induced toxicity in human umbilical vein endothelial cells (HUVECs). Specifically, quercetin reduces the levels of GRP78, CHOP, and caspase-3 [136] to effectively regulate ERS. Additionally, quercetin can enhance mitochondrial autophagy by modulating the expression of SIRT1 and transmembrane BAX inhibitor-1 motif-containing 6 (TMBIM6) to suppress hypoxia/reoxygenation-mediated ROS generation. This eventually inhibits oxidative stress damage [86]. The stress-responsive kinase Pak2 gene-deficient mice models showed that quercetin can alleviate ER dysfunction through the IRE1/XBP1s signaling pathway [137]. Moreover, Shu et al. [138] demonstrated that quercetin can significantly scavenge free radicals, reduce lipid peroxidation, and improve peroxidase activity. Quercetin reduces GRP78, p-PERK, and p-eIF2α levels, increases HO-1 expression, and thus mitigates ERS via the PI3K/Akt signaling pathway (Fig. 5 and Table 1), improving cardiomyocyte survivability and reducing cardiac injury incidence.

5.1.19. Salidroside

Salidroside (Fig. 4), a phenylpropanoid glycoside obtained from *Rhodiola rosea Linn* [139], is reputed for its various pharmacological effects, and it is considered defensive against ischemic heart disease [140]. ERS and stress-induced apoptosis were curtailed in cardiomyocytes [88]. Pre-administration of Salidroside in a myocardial I/R rat model conspicuously reduced the extent of the infarction and decreased serum creatine kinase and lactate dehydrogenase levels. Salidroside seems to protect the injured myocardium by activating the AMPK signaling pathway, attenuating ERS, and ameliorating apoptosis [87] (Fig. 5 and Table 1).

5.1.20. Sulforaphane

Sulforaphane (Fig. 4) is a dietary isothiocyanate that occurs naturally in cruciferous vegetables such as broccoli, cabbage, and cauliflower [141]. It has been found to suppress proteins involved in ERS-dependent apoptosis, namely, GRP78, CHOP, and caspase-12, using a model of I/R-induced injury in newborn rat cardiomyocytes [142]. Sulforaphane activates the SIRT1 pathway, which reduces I/R injury. By inhibiting the UPR and decreasing activation of the PERK/eIF2α pathway, SIRT1 protects cardiomyocytes from ERS-induced death [89] (Fig. 5 and Table 1). Moreover, sulforaphane's role in reducing ERS helps to improve the viability of cardiomyocytes by reducing damage to the mitochondrial membrane potential, lowering the Bcl-2/Bax ratio, and preventing the activity of caspase-3.

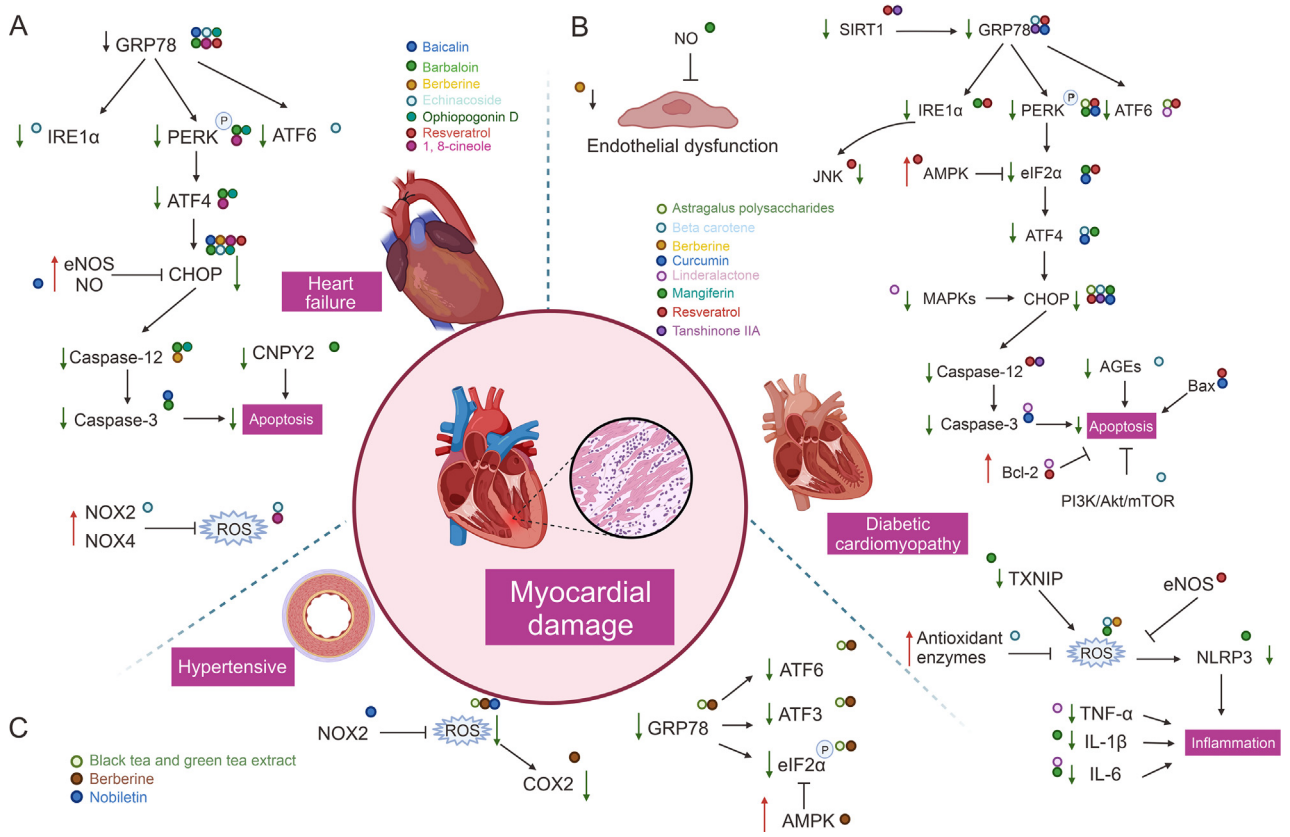

Fig. 6. Natural products target endoplasmic reticulum stress (ERS) mediated myocardial injury (MI) in heart failure, diabetic cardiomyopathy (DCM) and hypertensive. GRP78: glucose rregulated protein78; IRE1: inositol-requiring enzyme 1; PERK: protein kinase RNA (PKR)-like endoplasmic reticulum (ER) kinase; ATF6: activating transcription factor 6; ATF4: activating transcription factor 4; CHOP: CCAAT/enhancer-binding protein homologous protein; eNOS: endothelial-type nitricoxide synthase; NO: nitric oxide; CNPY2: cardiomyocyte-specific protein canopy homolog 2; NOX2: (nicotinamide adenine dinucleotide phosphate oxidase) NADPH oxidase 2; NOX4: NADPH oxidase 4; ROS: reactive oxygen species; COX2: cyclooxygenase-2; SIRT1: silencing information regulator 1; GRP78: glucose regulated protein78; JNK: c-Jun N-terminal kinase; AMPK: 5′ adenosine monophosphate-activated protein kinase; eIF2α: eukaryotic translation initiation factor 2α; MAPKs: mitogen-activated protein kinases; Bcl-2: BCL2 apoptosis regulator; AGEs: advanced glycosylation end products; TXNIP: thioredoxin interacting protein; NLRP3: NLR family fyrin domain containing 3; TNF-α: tumor necrosis factor-α; IL-1β: interleukin 1beta; IL-6: interleukin-6; ATF3: activating transcription factor 3.

5.1.21. Tanshinone IIA

Tanshinone IIA (Fig. 4) can indirectly regulate ERS by regulating microRNAs, and directly regulate ERS-related proteins [90]. MicroRNAs are small noncoding RNA molecules that are involved in various physiological and pathophysiological processes, and are often used to control signaling via the control components of the signaling pathways, providing delicate and comprehensive regulation of cellular pathways. The expression of MiR-133 was significantly reduced in apoptosis of clostridium-treated cardiomyocytes, and upregulation of MiR-133 protected cardiomyocytes from apoptosis [143] (Fig. 5 and Table 1).

5.1.22. Tournefolic acid B

Tournefolic acid B (Fig. 4) is a novel compound derived from *Clinopodium chinense (Benth.) Kuntze*, a traditional Chinese medicinal herb widely recognized for its potent anti-inflammatory, hypoglycemic, anti-tumor and anti-radiation properties. Recent studies have found that tournefolic acid B exhibits potent antioxidant activity in hypoxic/reoxygenated H9c2 cells, regulating the levels of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px). Furthermore, tournefolic acid B has been shown to activate PI3K and Akt phosphorylation, inhibiting the production of CHOP and caspase-12, thus reducing apoptosis generated by ERS (Fig. 5 and Table 1). Moreover, it increases the Bcl-2/Bax ratio, reduces JNK phosphorylation and has a protective effect on damaged myocardium [91].

5.2. Natural products target ERS mediated MI in cardiac remodeling and heart failure

5.2.1. Baicalin

For centuries, *Scutellaria baicalensis Ge*orgi roots have been extensively used in traditional medicine to promote overall wellness, reduce inflammation, and fight infections [144]. The compound baicalin, which originates from the roots of *Scutellaria baicalensis Georgi*, has demonstrated several beneficial effects in neonatal rat cardiomyocytes, such as restoring the activity of endothelial-type nitric oxide synthase (eNOS) and enhancing nitric oxide (NO) bioavailability, as well as mitigating clathrin-induced ERS-induced death by downregulating the pro-apoptotic protein CHOP [92]. Moreover, baicalin (Fig. 4) exhibited the potential to alleviate cardiomyocyte apoptosis, counteract MI, and improve left ventricular remodeling through a reduction in the expression levels of GRP78, GRP94, and caspase-3, as demonstrated in research [145] (Fig. 6A and Table 1).

5.2.2. Barbaloin

Aloe, a succulent plant belonging to the lily family and the genus *Aloe*, is known to possess anti-inflammatory, antioxidant, and immune-boosting properties. While historically used as TCM for treating digestive disorders, recent research highlights its potential use in treating cardiovascular disease through the compound barbaloin [146]. Barbaloin (Fig. 4) has been shown to modulate the

expression of ERS and pro-apoptosis-related proteins, including GRP78, PERK, p-PERK, ATF4, CHOP, caspase-3, and caspase-12, which help reduce cardiomyocyte injury. Notably, barbaloin may exert cardioprotective effects by reducing cardiomyocyte apoptosis through the cardiomyocyte-specific protein canopy homolog 2 (CNPY2) [93] (Fig. 6A and Table 1).

5.2.3. Berberine

In a rat model of myocardial infarction, berberine inhibited cardiac remodeling in post-infarction heart failure by attenuating MI and inhibiting cardiomyocyte apoptosis through the inhibition of ERS and modulation of CHOP and caspase-12 apoptotic pathways [94] (Fig. 6A and Table 1).

5.2.4. Echinacoside

Echinacoside (Fig. 4), the natural phenylethane glycoside found in the TCM Cistanche deserticola, has been shown to possess potent antioxidant and anti-inflammatory effects [147]. In an isoprenaline-induced heart failure model, echinacoside was observed to inhibit the expression of ERS pro-apoptotic proteins, including GRP78, p-IRE1α, p-PERK, ATF6, and CHOP, which in turn suppressed cardiomyocyte apoptosis. Additionally, echinacoside down-regulated the expression of nicotinamide adenine dinucleotide phosphate oxidase (NADPH) oxidase 2 (NOX2) and NADPH oxidase 4 (NOX4), reduced ROS levels (Fig. 6A and Table 1), and improved cardiac function by protecting the damaged myocardium from further injury [95].

5.2.5. Ophiopogonin D

Ophiopogon japonicus is a renowned traditional Chinese medicinal herb that is known to nourish yin, moisten the lungs, and alleviate cough. Of the many active ingredients present in the herb, ophiopogonin D (Fig. 4) has exhibited significant biological activity that enhances cardiovascular function while possessing anti-inflammatory, antioxidant, and anti-aging properties. When isoproterenol was used to induce ERS in rat cardiomyocytes, the expression of BiP, PERK, and ATF4 were notably upregulated. Furthermore, the expression of pro-apoptotic molecules, such as CHOP, Bax, and caspase-12, were also elevated. However, pretreatment of the H2c9 cell line with maitake saponin effectively suppressed the upregulation of these molecules (Fig. 6A and Table 1). As a result, the cardiomyocytes maintained their ER Ca^{2+} homeostasis, experienced reduced apoptosis, and alleviated MI [96].

5.2.6. Resveratrol

Resveratrol (Fig. 4) is a polyphenol antioxidant present in red wine, grape seeds, and grape skins. It has been found to possess cardioprotective properties. In particular, resveratrol enhances the Bcl-2/Bax ratio and suppresses ERS proteins including CHOP, GRP78, and GRP94, thereby offering protection against isoproterenol-triggered cardiomyocyte hypertrophy and death [97]. The anthracycline antibiotic adriamycin is known for its efficacy against multiple types of cancers, but it causes heart failure and cardiac issues. H9c2 cardiomyocytes undergo apoptosis due to ERS, which is the source of anthracycline antibiotics like adriamycin. Nonetheless, resveratrol blocks the expression of ERS markers proteins (GRP78 and CHOP) and activates the SIRT1 pathway (Fig. 6A and Table 1), thereby restoring H9c2 cell viability against adriamycin induced cardiotoxicity [97].

5.2.7. 1, 8-cineole

1,8-cineole (Fig. 4) is the primary component of Sugemule-3, a monoterpene [148]. Studies have revealed the ability of 1,8-cineole to decrease isoproterenol (ISO)-induced apoptosis and enhance H9c2 cardiomyocyte survival after ISO injury. To protect injured myocardium and lower cardiomyocyte apoptosis, 1,8-cineole primarily controls ERS and reduces the expression of pro-apoptotic proteins (GRP78, PERK, ATF4 and CHOP) associated with ROS generation (Fig. 6A and Table 1). Additionally, 1,8-cineole has been shown to alleviate ISO-induced cardiac injury and reduce cardiac hypertrophy, cytoplasmic vesicle formation, myofiber loss, and fibrosis. The findings of this study lay the foundation for potential treatments of cardiac hypertrophy-associated diseases, such as heart failure [98].

5.3. Natural products target ERS mediated MI in DCM

5.3.1. Astragalus polysaccharides

Astragalus polysaccharides (Fig. 4) is the primary bioactive constituent extracted from *Radix Astragali* roots and is widely used in medicinal applications [149]. Research over the past two decades has shown astragalus polysaccharides to possess antioxidant, antidiabetic, and immunomodulatory activities. It has also exhibited cardioprotective effects against DCM [150]. In a rat model of DCM, astragalus polysaccharides was found to improve cardiac function and attenuate myocardial apoptosis primarily through modulation of the ERS pathway. Astragalus polysaccharides was able to down-regulate the expression of pro-apoptotic molecules such as ATF6 and PERK in the ER, while lentiviral overexpression of CHOP protein revealed that the protective effect of astragalus polysaccharides was blocked (Fig. 6B and Table 1). It is therefore hypothesized that astragalus polysaccharides may reduce cardiomyocyte apoptosis and protect damaged myocardium by decreasing the expression of pro-ERS proteins [99].

5.3.2. Beta carotene

Beta-carotene (Fig. 4) is a well-known precursor to vitamin A, present in a variety of fruits and vegetables and has been suggested to decrease the incidence of cancer and cardiovascular disease [151]. DCM is characterized by cardiac dysfunction due to the formation of advanced glycosylation end products (AGEs), resulting from protein glycosylation [152]. H9c2 cell assays showed that beta-carotene significantly inhibits AGEs-induced cell death and apoptosis, reducing intracellular ROS production and decreasing the rate at which antioxidant enzymes decompose. Furthermore, beta-carotene reduces the expression of pro-apoptotic and ERS proteins such as ATF4, GRP78, and CHOP via the PI3K/Akt/mTOR pathway (Fig. 6B and Table 1). It also reduces the incidence of ERS and autophagy and mitigates the damage to cardiomyocytes that is caused by oxidative stress [100].

5.3.3. Berberine

Berberine mitigated ROS production and downregulated the expression of proteins related to the ERS by suppressing oxidative stress and ERS, ultimately ameliorating the endothelial cell aberrations resulting from Kawasaki disease and diabetes [101,153] (Fig. 6B and Table 1).

5.3.4. Curcumin

Curcumin (Fig. 4) is a rhizome extract belonging to the class of *Curcumae Longae Rhizoma*. It is an agent of interest owing to its favorable pharmacological properties such as anticancer, anti-inflammatory, antidiabetic, and antioxidant benefits [154]. Curcumin has been found to be effective in treating different chronic conditions, including cardiovascular illnesses, autoimmune disorders, and different malignancies. In a palmitic acid (PA)-induced H9c2 cell model, curcumin was able to reverse the upregulation of ERS marker proteins and pro-apoptotic proteins (CHOP, GRP78, Caspase-3, Bax) [102] (Fig. 6B and Table 1).

Despite its many benefits, curcumin's hydrophobicity and volatility limit its use. However, recent research has revealed that the effects of curcumin can be significantly maximized by binding it to nanoparticles (curcumin-NPs). Curcumin-NPs reduced apoptosis in lipotoxic PA-treated cardiomyocytes and strongly upregulated the expression of LC3-II while suppressing the expression of p-PERK, p-eIF2α, and ATF4. This suggests that curcumin-NPs can prevent cardiomyocytes from undergoing apoptosis by blocking the ERS apoptotic pathway and stimulating the autophagy system [103].

5.3.5. Linderalactone

Linderalactone (Fig. 4), a sesquiterpene lactone extracted from the root of *Aconitum carmichaelii Debeaux*, shows great potential as a treatment for dilated cardiomyopathy [155]. Studies have revealed that linderalactone decreases ribosomal reduction, balloon-like degeneration, and ER dilatation - all processes related to ERS. In addition, it inhibits ERS mediated by the diabetes-activated MAPKs/ATF6 pathway (Fig. 6B and Table 1). Furthermore, linderalactone suppresses myocardial tissue hypertrophy as well as inflammatory responses in cardiomyocytes. As a result, it can be an effective therapy option to mitigate MI in DCM [104].

5.3.6. Mangiferin

Mangiferin (Fig. 4), a flavonoid found in mango, long-clawed I/Ris, or robinia has been extensively used in the treatment of diabetes [156]. Recent studies have shown that mangiferin can effectively reduce oxidative stress caused by ERS in EA.hy926 cells (human umbilical vein cell line) that were exposed to high glucose levels. This result is achieved by reducing ROS generation and attenuating IRE1α phosphorylation. Moreover, it also lowers the TXNIP levels and NLRP3 inflammatory vesicle activation, thereby decreasing the production of interleukin 1beta (IL-1β) and interleukin-6 (IL-6) and preventing inflammation. Increasing the generation of NO which helps in regulating endothelial homeostasis, mangiferin could potentially play a role in treating diabetic cardiovascular problems. Besides, mangiferin also protects the myocardium from ERS-induced injury by decreasing the activation of the PERK/eIF2α/ATF4/CHOP pathway while increasing SIRT1-mediated eIF2α deacetylation [105] (Fig. 6B and Table 1).

5.3.7. Resveratrol

It has been demonstrated that methoxylated resveratrol derivatives can improve endothelial dysfunction and have vasoprotective effects. These derivatives achieve this effect by reducing

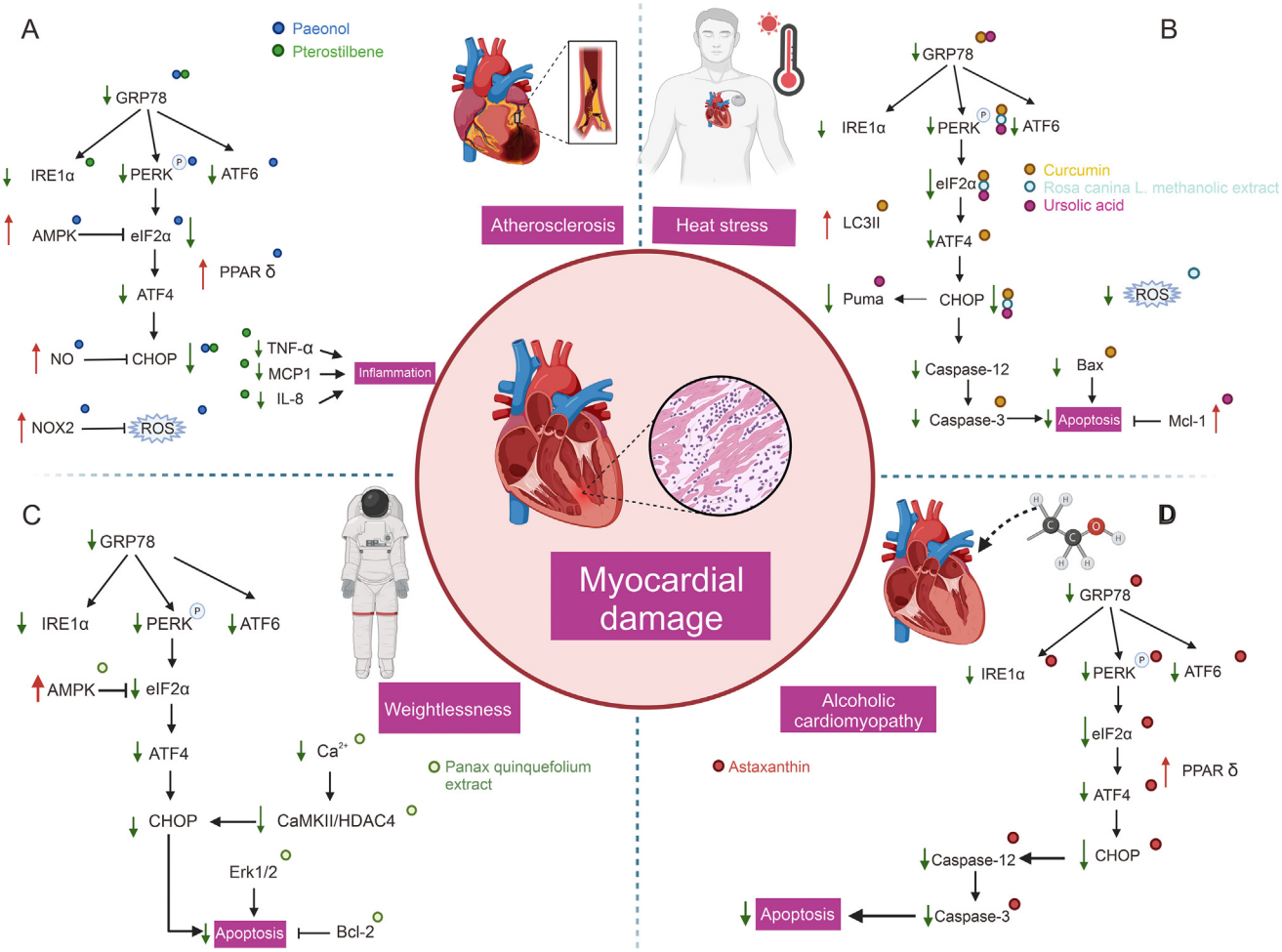

Fig. 7. Natural products target endoplasmic reticulum stress (ERS) mediated myocardial injury (MI) in atherosclerosis, heat stress, alcoholic cardiomyopathy and weightlessness. GRP78: glucose regulated protein78; IRE1: inositol-requiring enzyme 1; PERK:protein kinase RNA (PKR)-like ER kinase; ATF6: activating transcription factor 6; AMPK: 5′ adenosine monophosphate-activated protein kinase; eIF2α: eukaryotic translation initiation factor 2α; ATF4: activating transcription factor 4; PPAR δ: peroxisome proliferator activated receptor gamma; NO: nitric oxide; CHOP: CCAAT/enhancer-binding protein homologous protein; NOX2: nicotinamide adenine dinucleotide phosphate oxidase (NADPH) oxidase 2; ROS: reactive oxygen species; TNF-α, tumor necrosis factor-α; MCP1: monocyte chemoattractant protein-1; IL-8: interleukin 8; LC3II: microtubule associated protein 1 light chain 3 beta; Mcl-1: MCL1 apoptosis regulator, BCL2 family member; CaMKII: Ca^{2+}/calmodulin-dependent protein kinase II; HDAC4: histone deacetylase 4; Bcl-2: BCL2 apoptosis regulator.

oxidative stress and ERS through the AMPK/SIRT1/eNOS pathway [157]. Resveratrol also improves cardiac function, reduces cardiomyocyte apoptosis, and increases SIRT1 in diabetic rats. Moreover, it improves ERS through the PERK/eIF2α, ATF6/CHOP, and IRE1α/JNK pathways. Therefore, resveratrol is a potential treatment for DCM [106]. Remarkably, metal ions are also crucial to the cardioprotective action of resveratrol. By releasing Zn^{2+} and blocking the opening of the mitochondrial permeability transition pore, resveratrol suppresses the production of ER chaperone proteins such as GRP78/94, as well as ER apoptotic proteins like CHOP, caspase-12, and JNK [158] (Fig. 6B and Table 1).

5.3.8. Tanshinone IIA

Tanshinone IIA, the primary active component of Salvia miltiorrhiza, has been found to exhibit preventive properties against cardiovascular disease and diabetes [159]. One common complication in diabetic patients is DCM, which can lead to heart failure through abnormal glucolipid metabolism and induction of ERS [160]. Tanshinone IIA was observed to inhibit the activity of GRP78 through SIRT1, inhibit the expression of ERS-related proteins and mRNAs (Fig. 6B and Table 1), improve the pathological morphology of cardiomyocytes, reduce cellular mortality, and consequently slow down MI [107].

5.4. Natural products target ERS mediated MI in hypertensive

5.4.1. Black tea and green tea extract

In most Western countries, tea products made from the leaves of the tea tree (*Camellia sinensis*) are the primary source of total polyphenol intake [161]. Regular tea drinking has been linked to the prevention of cardiovascular disease and reversal of endothelial dysfunction [162]. During the fermentation process used to produce black tea, catechins are converted to theaflavins and thearubigin polymers [162]. Elevated homocysteine levels in hypertension patients cause endothelial cells to experience ERS [163]. Black tea extract (BT) and theaflavin-3,3′-gallate (TF3) have been shown to reduce endothelial damage linked to hypertension by reducing ERS. Treatment with BT extract and TF3 decreased levels of homocysteine metabolizing enzymes and ROS levels while also reversing the rise in aortic ERS indicators (activating transcription factor 3 (ATF3), ATF6, and eIF2α) elevation in rats given Ang II. Furthermore, this medication restored normal blood pressure in hypertensive rats and enhanced endothelium-dependent diastole in the aorta, carotid, and renal arteries. Therefore, black tea shows potential as a supplement for hypertensive patients as it has a distinct cardioprotective action and reduces vascular dysfunction [108]. On the other hand, green tea has an abundance of flavonoids that include catechins such as epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate [164]. Nicotine, the primary alkaloid in tobacco, causes cardiotoxic injury and toxicity in cardiomyocyte cultures. Rats treated with green tea extract and epigallocatechin gallate showed significant normalization in toxicity by decreasing the expression level of the chaperone stress marker GRP78, increasing catalase activity and ultimately reducing oxidative stress and apoptosis [165] (Fig. 6C and Table 1).

5.4.2. Berberine

Berberine was found to prevent ERS caused by myocardial ischemia-reperfusion in the heart and demonstrated antihypertensive benefits in rats with spontaneous hypertension [166]. In a rat model of renal vascular hypertension, berberine was shown to activate AMPK, leading to the inhibition of eIF2α phosphorylation, ATF3, ATF6, and XBP1 levels, as well as ROS-mediated cyclooxygenase-2 (COX2)-dependent contraction [109] (Fig. 6C and Table 1). These investigations provide further evidence of berberine's advantageous vascular effects in managing hypertension, which is critical for the prompt treatment of myocardial damage.

5.4.3. Nobiletin

Increased oxidative stress is a typical pathophysiologic response in pressure overload-induced cardiac hypertrophic diseases. Nobiletin (Fig. 4) which is a compound extracted from citrus fruit peels, possesses strong antioxidant properties [167]. *In vivo* experiments, Nobiletin significantly ameliorated pressure overload-induced cardiac hypertrophy by inhibiting GRP78, CHOP, and caspase-12 expression, and thus improving ERS in cardiac hypertrophy (Fig. 6C and Table 1). Moreover, Nobiletin's ability to reduce cardiomyocyte apoptosis may be attributed to its inhibition of NADPH oxidase. It has also been found that Nobiletin has a positive effect on cardiac hypertrophy as it alleviates ERS by inhibiting NOX2 expression, consequently reducing apoptosis. Thus, Nobiletin can attenuate the hypertrophic response of cardiomyocytes [110].

5.5. Natural products target ERS mediated MI in atherosclerosis

5.5.1. Paeonol

Paeonol (Fig. 4), a major phenolic component derived from peony bark, is widely used in TCM [168]. It has been found to enhance AMPK expression and PPAR δ activity in isolated mouse aortic cells and HUVECs, thereby alleviating ERS. Peoniflorin, on the other hand, inhibits the expression of ERS-related proteins (GRP78, ATF6, eIF2α, PERK). As a result, it reduces the overproduction of ROS, improves NO bioavailability, and alleviates vascular endothelial dysfunction [111,169] (Fig. 7A and Table 1).Additionally, paeoniflorin has been found to reduce NADPH subunits, further strengthening its therapeutic effect [170]. Furthermore, paeonol has been known to protect endothelial function in mice induced by clathrin *in vivo* by inhibiting ROS related to ERS via NOX2 [171].

5.5.2. Pterostilbene

Pterostilbene (Fig. 4) is a natural plant antitoxin found in blueberries displaying strong anti-inflammatory properties. In HUVECs, pterostilbene therapy demonstrated a reduction in ER-associated markers like GRP78, p-IRE1, and p-eIF2α, which are associated with inflammation induced by TNF-α. The reduced signaling of ERS diminished the expression of various inflammatory cytokines, including intercellular adhesion molecule-1 (ICAM1), interleukin-8 (IL-8), monocyte chemotactic protein-1 (MCP-1), soluble E-selectin, and matrix metalloproteinase 9 (MMP9) (Fig. 7A and Table 1). Ultimately, these changes exhibited by pterostilbene provide protection against inflammation in vascular endothelial cells [112].

5.6. Natural products target ERS mediated MI in other MI diseases

5.6.1. Heat stress

5.6.1.1. Curcumin. Curcumin mitigated HS (HS)-induced physiological disturbances in cardiac injury by reversing ER-mediated cardiomyocyte apoptosis, decreasing cardiac troponin I (cTn-I), and increasing cardiomyocyte Ang II levels, while reducing the expression of GRP78 and CHOP [113] (Fig. 7B and Table 1).

5.6.1.2. Rosa canina L. Methanolic extract. The Rosa canina extract possesses a wide range of medicinal benefits, such as its antioxidant, antimicrobial, anticancer, antidiabetic, anti-inflammatory, and immunomodulatory effects [172]. *In vivo* experiments revealed that treatment with Rosa canina extract effectively reduced the overproduction of ROS induced by HS in cardiomyocytes. Specifically, heat-stressed cardiomyocytes

demonstrated increased expression of pro-apoptotic proteins, including CHOP, caspase 8, p-PERK, and p-eIF2α, while Rosa canina extract was able to effectively inhibit the expression of these pro-apoptotic proteins (Fig. 7B and Table 1), thereby providing a protective effect upon injured myocardium that has been exposed to HS [114].

5.6.1.3. Ursolic acid. HS has been found to be associated with multiple cardiovascular disorders and it severely hampers the functioning of cardiomyocytes [173]. The principal mechanism behind apoptosis induced by HS is the activation of the PERK-eIF2α-CHOP UPR, which results in increased production of the Puma protein. Ursolic acid (Fig. 4) safeguards the cells by restoring the intracellular redox state, triggering production of the anti-apoptotic protein MCL1 apoptosis regulator, BCL2 family member (Mcl-1), and blocking CHOP-induced overexpression of Puma. Ursolic acid supplementation is believed to be an effective measure in reducing the harmful impacts of HS on cardiomyocytes, given its antioxidant and anti-apoptotic properties against cardiac injury caused by ERS [115] (Fig. 7B and Table 1).

5.6.2. Weightlessness

5.6.2.1. Panax quinquefolium extract. Upon exposure to microgravity, studies have demonstrated the occurrence of cardiac shrinkage and MI. However, the beneficial effects of panax quinquefolium on heart remodeling induced by weightlessness have also been demonstrated. Specifically, panax quinquefolium has been found to notably reduce serum CK-MB, cTnT, and ischemia-modified albumin (IMA) levels. Moreover, it exerts a positive effect by activating AMPK, while simultaneously inhibiting the Erk1/2 and CaMKII/HDAC4 signaling pathway stress and Ca^{2+} overload (Fig. 7C and Table 1). As a result, panax quinquefolium leads to structural improvement of the impaired cardiac structure, while also decreasing weightlessness-induced cardiomyocyte apoptosis [117].

5.6.3. Alcoholic cardiomyopathy (ACM)

5.6.3.1. Astaxanthin. Astaxanthin (Fig. 4) belongs to the family of lutein, an oxygenated derivative of carotenoids. Studies have indicated the protective effects of astaxanthin on myocardial damage and anti-apoptosis [174]. Recently, astaxanthin has been found to reduce the accumulation of fat and glutamate-induced apoptosis by reducing ERS [175]. Chronic use of ethanol results in ACM, in which cardiac damage plays a crucial role in its progression. The development of ethanol-induced cardiomyocyte damage is associated with ERS. *In vivo* and *in vitro* investigations in ACM, reveal that astaxanthin may inhibit the activation of the PERK-eIF2α-ATF4, ATF6, and IRE1-XBP1 ERS signaling pathway induced by ethanol, leading to reduced expression of pro-apoptotic proteins, e.g., GRP78, CHOP, and caspase-12 (Fig. 7D and Table 1). As a result, it may reduce myocardial morphological changes and cardiac damage in dilated cardiac remodeling [116].

6. Discussion

In recent years, there has been a rapid increase in studies targeting natural agents to ameliorate MI by targeting ERS. Particularly in hypoxia/reperfusion injury, numerous natural products have shown potential therapeutic effects, providing new ideas for drug development for MI. Additionally, the innovation of new drug delivery modes has attracted extensive attention from researchers, with nanoparticle drug delivery emerging as a promising field for the treatment of MI. Innovative drug delivery routes can improve the accuracy and efficacy of drug-targeted therapy, and curcumin nanoparticles have been demonstrated to be highly effective in treating MI-related diseases. Studies have confirmed the ability of curcumin-loaded nanoparticles to ameliorate cardiomyocyte injury and reduce apoptosis via AMPK [176], modulation of autophagy, and slowing down of ERS-related pathways [177,178]. Natural products such as resveratrol [179], icariin [180], and notoginsenoside R1 [181] have also been applied in new drug delivery pathways and shown to have potential in targeting damaged myocardium and providing myocardial protection and repair.

However, research on natural drugs targeting ERS to ameliorate MI still has many deficiencies. While many studies have shown that drugs can affect the expression of ERS and apoptosis-related proteins, they have not elucidated the specific mechanisms through which natural small molecules affect protein expression. Further studies should focus on the direct mechanism of the action of natural drugs, including their effects on protein modification, gene transcription, and protein binding. This will lead to a more accurate understanding of the mechanism of action of natural drugs, promoting clinical trials and applications while minimizing safety risks and maximizing the therapeutic effects of natural drugs on MI.

Furthermore, our literature review has revealed that studies on MI by natural compounds require more standardization, with modeling methods, dosage, start time, and duration of drug administration all needing to be standardized. As such, future research must adopt more rigorous and standardized experimental designs, including the use of multiple cellular models to validate findings. *In vivo* and *in vitro* experiments are also essential for comprehensive results, while the control of dosage and duration of drug administration is crucial in ensuring accurate and reliable findings.

Encouragingly, other factors contributing to MI, such as metabolic abnormalities, heat stress, and weightlessness, are gaining more attention from researchers. Such a shift in focus is vital in improving MI of different etiology and providing new ideas and reference for the pharmacological treatment of MI.

7. Conclusions and perspectives

ERS is a biological response to changes in internal and external environments that occur when these environments change beyond a specific threshold. ER plays a crucial role in multiple regulatory mechanisms that impact the cardiovascular system, serving as the first site of cellular stress response. Unresolved ERS can cause cardiomyocytes and vascular cells to malfunction and undergo apoptosis, leading to reduced systolic and diastolic functions of the heart that can potentially cause heart failure. Given the role of ERS and its convergence in multiple pathogenic pathways, natural products with antioxidant, anti-inflammatory, and anti-apoptotic properties offer protection to cardiomyocytes from damage and death. Natural solid substances, such as polyphenols, alkaloids, saponins, and other phytochemicals, can reduce ERS by acting on various signaling pathways linked to the generation of ROS, inflammation, and apoptosis.

Despite the tremendous potential of natural compounds for treating MI, misconceptions about their use still abound. Firstly, their lack of standardization in dosage, potency, and purity makes using natural compounds challenging. This lack of standardization can lead to variability in therapeutic effects as well as potential safety issues. Secondly, natural compounds may interact with conventional medications, leading to adverse reactions or reduced efficacy. Hence, clinicians should consider potential drug interactions when combining herbal monomers with other drugs. Thirdly, while natural compounds are generally considered safe, high doses or prolonged use may still pose risks. Some herbal monomers have been reported to cause adverse reactions such as allergic reactions, gastrointestinal disturbances, and hepatotoxicity. Besides, since MI is a serious disease that requires comprehensive

treatment and management, natural medicines are not complete substitutes for conventional medical treatments, and it is dangerous to forgo or delay receiving formal treatment. Finally, despite growing evidence supporting the therapeutic potential of herbal monomers, there are still research gaps in their mechanism of action, long-term safety, and optimal dosing regimen. Therefore, it is necessary for researchers to address these misconceptions in future studies to avoid safety risks and realize the full potential of natural medicines in MI.

The study of natural products that target ERS is still in its early stages despite the promising use of these agents in the prevention and treatment of cardiovascular disorders. Further research is required to fully understand the mechanism and impact of natural products that targetERS and to develop fresh concepts and approaches for managing cardiovascular disorders. Clinical trials are also required to confirm the efficacy and safety of natural products in managing cardiovascular disorders.

CRediT authorship contribution statement

Kai Yang: Writing – original draft. **Ping Zhang:** Writing – original draft. **Jixin Li:** Writing – review & editing. **Genming Zhang:** Writing – original draft. **Xing Chang:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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