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Review Article

Protective effects of Chinese herbal monomers against ischemia-reperfusion injury

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Abstract: Objectives: Ischemia-reperfusion injury is a complicated pathologic process that involves multiple factors including oxidative stress, endoplasmic reticulum stress, calcium overload, inflammatory response, disturbances in energy metabolism, apoptosis, and some newly-described forms of programmed cell death (e.g., necroptosis, autophagy, pyroptosis, patanatos, and ferroptosis). Chinese herbal monomers (CHMs) have long been applied to treat ischemia-reperfusion injury based on a solid research foundation. This paper objectively reviews in vitro and in vivo studies on the use of CHMs to protect against ischemia-reperfusion injury. Methods: We reviewed 31 CHMs that have been shown to be effective for treating ischemia-reperfusion injury models of the heart, brain, and kidney. According to the mechanism of action, these CHMs were divided into three categories: protecting damaged histocytes, inhibiting inflammatory cells, and promoting the proliferation of damaged histocytes. Some CHMs were found to have more than one mechanism at the same time. Results: Of the 31 CHMs, 28 protect damaged histocytes, 13 inhibit inflammatory cells, and three promote the proliferation of damaged histocytes. Conclusions: CHMs show promise for treating ischemia-reperfusion injury. The eexisting treatment experiences for ischemia-reperfusion injury can be used as a reference.

Keywords: Chinese herbal monomers, ischemia-reperfusion injury, myocardial infarction, cerebral infarction, renal transplantation

Introduction

Ischemic diseases have recently risen to the top of the list of global killers and disablers [1-3]. A wide variety of ischemic diseases, including acute myocardial infarction, ischemic stroke, and acute renal injury, are observed clinically. Ischemia is the lack of blood supply to histocytes. The lack of nutrients and oxygen may cause destruction of the histocytes, leading to the complete loss of organ function. Previous therapeutic studies focused on the rapid restoration of blood supply. Histocyte injury and organ failure can result from ischemia along with reperfusion after the restoration of blood supply, which is called ischemia-reperfusion injury [4]. Thus, reperfusion therapy is a double-edged sword that complicates the treatment and prevention of ischemic disorders.

The pathologic mechanisms of ischemia-reperfusion injury are complex and involve oxidative stress, endoplasmic reticulum (ER) stress, calcium overload, inflammatory response, disturbances in energy metabolism, apoptosis, and some forms of programmed cell death (e.g., necroptosis, autophagy, pyroptosis, patanatos, and ferroptosis) [5]. Therefore, adjunctive interventions are needed to limit the adverse consequences of ischemia-reperfusion injury. Traditional Chinese medicines have attracted considerable attention due to their holistic approach to therapy and the benefits of having sev-

eral targets, multiple sessions, and multiple pathways. Monomers, which are key components of most Chinese herbal extracts, provide a variety of medical benefits. Chinese herbal monomer (CHM) has been shown to prevent ischemia-reperfusion injury in a number of animal trials and clinical studies [5-8]. Due to its all-natural components, low cost, and low toxicity, CHM has become a focus of current research, including studies on the use of CHM in ischemic disorders.

This review discusses the therapeutic and preventive mechanisms of CHM in myocardial ischemia-reperfusion injury (MIRI), cerebral ischemia-reperfusion injury (CIRI), and renal ischemia-reperfusion injury (RIRI) based on three mechanisms (the inhibition of death signaling, inhibition of inflammatory response, and promotion of histocytes proliferation), and highlights the prospects of CHM in the prevention and treatment of ischemia-reperfusion injury.

Protection of damaged histocytes

Luteolin is a natural soluble flavone found in green vegetables, perilla leaf, and chamomile tea. Luteolin suppressed the activation of the p38 Mitogen-Activated Protein Kinases (p38 MAPK) signaling pathway in a rat MIRI model. By suppressing this signaling pathway, luteolin reduced apoptosis in cardiomyocytes by inhibiting the expressions of bcl-2-Associated X Protein (Bax) and cysteinyl aspartate specific proteinase (caspase)-3 and increasing B-cell lymphoma-2 (Bcl-2) expression [9]. Luteolin inhibited pyroptosis during MIRI in rat and cell models by suppressing the nuclear factor-kappaB (NF-κB)/NOD-like receptor thermal protein domain associated protein 3 (NLRP3) signaling pathway, as evidenced by reductions in apoptosis-associated speck-like protein containing (ASC) and caspase-1 expressions [10].

Dihydroquercetin, a dihydroxyflavone, is the major active ingredient in the root of *Larix gmelinii*. Dihydroquercetin inhibited MIRI in rat and cell models. The mechanism of its protective effect may be by activating the Phosphatidylinositol-4,5-bisphosphate 3-kinase/protein kinase B (PI3K/Akt) signaling pathway to reduce oxidative stress-induced apoptosis by upregulating nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) activation and hemeoxygenase 1 (HO-1) expressions. The mechanism may also involve ER stress-induced apoptosis by inhibiting the expressions of c-Jun N-terminal kinase (JNK), downstream C/EBP homologous protein (CHOP), Bax, and caspase-12 and increasing Bcl-2 expression [11].

Curculigoside is the major bioactive ingredient in *Curculigo orchioides Gaertn*. In rat and cell MIRI models, curculigoside decreased mitochondria-mediated apoptosis by closing mitochondrial permeability transition pores. Moreover, curculigoside significantly decreased the expressions of cytoplasmic (cyt-c), caspase-9, and caspase-3 in damaged myocardial cells [12].

Icariin is a major active ingredient in *Epimedium*. In rat and cell models, icarin may protect against MIRI by activating the sirtuin 1 (SIRT1)/forkhead box-1 (FoxO1) signal pathway, inhibiting mitochondrial oxidative stress by decreasing malondialdehyde (MDA) and reactive oxygen species (ROS), increasing superoxide dismutase (SOD) activity, and inhibiting apoptosis by increasing Bcl-2 expression while decreasing the expressions of Bax, cyt-c, and caspase-3 [13].

Matrine is a quinolizidine alkaloid extracted from the root of *Sophora alopecuroides, Sophora tonkinensis*, and *Sophora flavescens*. Matrine inhibited apoptosis during MIRI in a rat model by activating the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway, which decreased the expression of Bax and increased the expression of Bcl-2 [14].

Platycodin D is a main active saponin in *Platycodon grandiflorum*. Platycodin D showed protective effects during MIRI in a cell model by activating Akt/Nrf2/HO-1-mediated signaling, reducing oxidative stress by decreasing the levels of reactive oxygen species (ROS) and malondialdehyde (MDA), increasing the expressions of SOD and catalase (CAT), and reducing apoptosis by increasing the expression of Bcl-2 levels while decreasing those of Bax and caspase-3 [15].

Quercetin is a flavonoid isolated from plant flowers, leaves, and fruits. Quercetin can effectively upregulate the expression of Bcl-2 and downregulate the expression of Bax by activating the SIRT1/peroxisome proliferator-activated receptor-gamma co-activator (PGC)-1α signaling pathway, resulting in anti-apoptotic effects during MIRI in rat and cell models [16].

Schisandrin B is isolated from the fruit of *Schisandra chinensis*. Schisandrin B reduces oxidative stress by decreasing MDA expression and increasing SOD expression. Schisandrin B alleviates ER stress by inhibiting activating transcription factor 6 (ATF 6), protein kinase RNA-like endoplasmic reticulum kinase (PERK), and CHOP to suppress apoptosis during MIRI in a rat model induced by decreased Bax, caspase-9, and caspase-3 levels and increased Bcl-2 level [17].

Salvianolic acid A is a polyphenolic compound isolated from the root of *Salvia miltiorrhiza*. Salvianolic acid A inhibited oxidative stress during RIRI in rat and cell models by increasing the SOD level while decreasing the MDA and ROS levels. Salvianolic acid A inhibited apoptosis through the activation of the Akt signaling pathway by increasing the Bcl-2 level and decreasing caspase-3 activation [18].

Salvianolic acid B is a water-soluble component isolated from *Salvia miltiorrhiza Bunge*. Salvianolic acid B inhibited apoptosis during MIRI in a rat model by activating the PI3K/Akt signaling pathway, decreasing Bax expression, and increasing the Bcl-2 level [19]. Salvianolic acid B inhibited oxidative stress during RIRI in a rat model through the activation of the PI3K/Akt signaling pathway, as indicated by decreased MDA and ROS levels and increased SOD, CAT, and glutathione (GSH) activities [20].

Tanshinone IIA is a major active compound isolated from the root of *Salvia miltiorrhiza Bunge*. Tanshinone IIA inhibited apoptosis during MIRI in rat, mice, and cell models, such as the expressions of Bax, cyt-c, and caspase-3, while upregulating the expression of Bcl-2, as well as inhibited oxidative stress such as decreased MDA and ROS levels play protective roles [21]. Meanwihle, tanshinone IIA blocked mitochondrial apoptosis by activating the SIRT/PGC-1α signaling pathway during MIRI in mice and cell models. Tanshinone IIA decreased the production of mitochondrial ROS, reduced the expressions of pro-apoptotic proteins such as Bax and caspase-9, increased the expressions of anti-apoptotic factors such as Bcl-2, and X-linked inhibitor of apoptosis (X-IAP), and limited the leakage of mitochondrial cyt-c [22]. However, during CIRI in mice and cell models, tanshinone IIA increased the activities and the contents of total-antioxidant capacity, SOD, CAT, and glutathione peroxidation (GSHpx). It attenuates the level of ROS, MDA, 8-Hydroxy-2-deoxyguanosine (8-OHdG), as well as the carbonyl and nitrotyrosine protein contents through the antioxidant signaling pathway mediated by Nrf2 activation to reduce oxidative stress [23].

Astragaloside IV is an active saponin extracted from *Astragalus membranaceus* and *Radix Astragali*. The protective effect of astragaloside IV against MIRI in rat and cell models was associated with the activation of extracellular signal-regulated kinase (ERK) and subsequent reduction of apoptosis by decreasing the Bax and caspase-3 levels and increasing the Bcl-2 level [24]. Astragaloside IV inhibited the MAPK signaling pathway along with downstream p38 by regulating microRNA-101a/transforming growth factor (TGF)βR1/toll-like receptor (TLR)2 axis, thus attenuating apoptosis during MIRI in a cell model [25]. During CIRI in mice and cell models, astragaloside IV activated Akt to promote hexokinase-II (HK-II) binding to mitochondria, thereby protecting neurons from apoptosis and DNA damage. Meanwhile, astragaloside IV reduced the release of apoptosis-inducing factor (AIF) by inactivating poly-ADP-ribose polymerase-1 (PARP-1), thereby protecting neurons from parthanatos [26]. Astragaloside IV prevented oxidative stress by increasing the SOD activity while decreasing the activities of MDA and ROS. Astragaloside IV inhibited neuronal apoptosis by activating the JAK/STAT signaling pathway during CIRI in rat and cell models [27].

Baicalin is a flavonoid derived from the root of *Scutellaria baicalensis Georgi*. Baicalein inhibited apoptosis during MIRI in a rat model by increasing the Bcl-2 level and decreasing the Bax and caspase-3 levels [28]. The protective effect of baicalin against MIRI in the rat and cell

models was associated with the downregulation of calcium-sensing receptor (CaSR), activation of ERK, and subsequent reduction of apoptosis [29]. Baicalin protected cardiac microvascular endothelial cells during MIRI in a rat model by activating the PI3K/Akt pathway to promote the release of nitric oxide and cyclic guanosine monophosphate. Baicalin also reduced necroptosis by inhibiting the expressions of receptor-interacting protein (RIP) 1, RIP3, and mixed-lineage kinase domain (MLKL) [30]. In rat and cell models of CIRI, baicalin inhibited the activation of PARP-1 and reduced the release of AIF to attenuate parthanatos, reduce oxidative stress, restore mitochondrial membrane potential, protect mitochondrial function, and protect cerebral tissues from ischemic injury [31].

Ginsenoside Rb1 is a major effective ingredient of *Panax ginseng C. A. Mey*. Ginsenoside Rb1 had a protective effect against apoptosis in a rat model of MIRI by inactivating the Ras homolog gene family member A (RhoA)/Rho-associated coiled-coil containing kinase 1 (ROCK1) signaling pathway, resulting in increased Bcl-2 production and decreased Bax, caspase-3, and caspase-9 production [32].

Curcumin is a polyphenol from *Curcuma longa*. Curcumin can relieve oxidative stress by increasing the SOD activity while decreasing the levels of MDA and ROS. Curcumin inhibited apoptosis in a cell model of MIRI by reducing ER stress, suppressing the MAPK/ERK and MAPK/JNK signaling pathways, and decreasing the expression of CHOP [33].

Senkyunolide-H is a major bioactive component in *Ligusticum chuanxiong Hort*. In mice and cell models of CIRI, senkyunolide-H stimulated the PI3K/Akt signaling pathway to inhibit apoptosis by increasing the B-cell lymphoma-extra large (Bcl-XL) level and decreasing caspase-3 activation [34].

Gastrodin is a phenolic compound extracted from *Gastrodia elata Blume*. Gastrodin protected against oxidative stress in rat and cell models of CIRI by activating the Nrf2/ARE signaling pathway and increasing the expressions of HO-1, NADPH-quinone oxidoreductase (NQO-1), and brain-derived neurotrophic factor (BDNF) [35].

Tetrahydroxystilbene glucoside is the main active ingredient of *Fallopia multiflora*. In mice model of CIRI, tetrahydroxystilbene glucoside prevented oxidative stress by increasing SOD activity and decreasing the expressions of MDA and ROS. Tetrahydroxystilbene glucoside inhibited brain neuron apoptosis by effectively suppressing the activation of caspase-3 and caspase-9. Tetrahydroxystilbene glucoside alleviated brain neuronal autophagy by effectively reducing the levels of beclin1 and microtubule associated protein 1 light chain 3 (LC3) II [36].

Puerarin is the major ingredient in the root of *Pueraria lobata*. In a cell model of MIRI, puerarin inhibited autophagy by decreasing the expression of LC3 II as well as beclin1 upregulation mediated by activation of Akt [37].

Artemisinin is a sesquiterpene lactone from *Artemisia annua*. In a rat model of MIRI, artemisinin inhibited autophagy by reducing the expressions of autophagy-related gene 5 (Atg5) and LC3 II [38].

Tanshinone I is a major ingredient in *Salvia milorrhiza Bunge*. In rat and cell models of MIRI, tanshinone I decreased the ROS level and inhibited oxidative stress by activating the Akt/Nrf2 pathway, promoting the activation of Akt, and enhancing the expressions of anti-oxidative factors (namely, NQO-1 and HO-1). Tanshinone I can prevent oxidative stress by increasing SOD activity and decreasing the MDA activity. Also, tanshinone I protects against necroptosis by restraining the RIP1, RIP3, and MLKL levels [39].

Emodin, an anthraquinone derivative, is the major active ingredient from the rhizome of *Rheum palmatum*. In rat and cell models of MIRI, emodin inhibited pyroptosis by inhibiting the NF-κB/NLRP3 signaling pathway, as evidenced by reductions in the expression of ASC, caspase-1, and gasdermin D [40].

Galangin is a polyphenolic compound extracted from Chinese herbs such as *Alpinia officinarum Hance*, *Plantago major L*, and *Scutellaria galericulata L*. In a gerbil model of CIRI, galangin inhibited ferroptosis by activating the solute carrier family 7 member 11 (SLC7A11)/glutathione peroxidase 4 (GPX4) axis, decreasing ROS production, and reducing oxidative stress [41].

Gastrodian is the major active ingredient from the dried tuber of *Gastrodia elata Bl*. In mice and cell models of MIRI, gastrodian inhibited pyroptosis by inhibiting the NLRP3/caspase-1 signaling pathway, as evidenced by reduced gasdermin D expression [42].

Hydroxysafflor yellow A is major active component from safflower. In rat and cell models of CIRI, hydroxysafflor yellow A suppressed the NF-κB signaling pathway and inhibited the expressions of NLRP3, ASC, caspase-1, and gasdermin D to alleviate ischemia-reperfusion injury by inhibiting the pyroptosis signaling pathway [43]. Hydroxysafflor yellow A also protected against autophagy in a rat model of CIRI by decreasing the expressions of E1B 19 kDa interacting protein 3 (BNIP3) and LC3 [44].

Oleanolic acid, a natural triterpenoid, is the major active ingredient in various food products including vegetable oils and the leaves and roots of *Olea europaea, Viscum album L*., and *Aralia chinensis L*. Oleanolic acid inhibited oxidative stress in a rat model of RIRI by activating the Nrf2/glutamate-cysteine ligase catalytic subunit (GCLc) signaling pathway, as indicated by the decreased MDA level and increased SOD, CAT, and GSH activities. Oleanolic acid inhibits apoptosis in a rat model of RIRI by decreasing the level of caspase-3 [45].

Magnolol is an active ingredient from the bark of *Magnolia officinalis*. In a rat model of RIRI, magnolol inhibited apoptosis by activating the Akt and ERK signaling pathways while suppressing the p38 and JNK signaling pathways, as evidenced by the increased level of Bcl-2 and decreased levels of Bax and caspase-3 [46].

Apigenin is a natural active ingredient found in many fruits and herbs such as oranges, onions, and parsley. In rat and cell models of RIRI, apigenin inhibited apoptosis increasing the Bcl-2 level and decreasing the levels of Bax and caspase-3 to activate the PI3K/Akt signaling pathway [47].

Inhibition of inflammatory cells

Luteolin inhibited inflammatory response in rat and cell models of MIRI by inhibiting the Toll-like receptor 4 (TLR4)/myeloid differentiation primary response 88 (MyD88)/NF-κB/NLRP3 inflammasome pathway, as evidenced by reductions in the levels of interleukin (IL)-1β, IL-18, and tumor necrosis factor (TNF)-α [10].

Tanshinone I lowered the amount of white blood cells, including neutrophils and lymphocytes, in blood in rat and cell models of MIRI. Tanshinone I also exerted inhibitory effects on TNF-α and IL-6. Therefore, tanshinone I can reduce the immune response and inflammation during MIRI [39].

Artemisinin inhibited inflammation in a rat model of MIRI by decreasing the NLRP3 inflammasome, as indicated by decreased NLRP3, ASC, caspase-1, and IL-1β levels [38].

Baicalin inhibited the inflammatory response in a rat model of MIRI by decreasing neutrophil infiltration, decreasing the expressions of inducible nitric oxide synthase (iNOS), IL-1β, and IL-6, and increasing the expressions of arginase-1 (Arg-1), IL-10, and TGF-β which alters the macrophage phenotype (from M1 to M2) [28].

Puerarin attenuated inflammation by decreasing the levels of TNF-α, IL6, and IL-1β in a cell model of MIRI [37]. The protective effect of puerarin may be related to the inhibition of inflammatory response through the SIRT1/NF-κB signaling pathway, as manifested by reduced levels of NF-κB, NLRP3, caspase-1, IL-1β, and IL-18 [48].

Salvianolic acid B may protected against the inflammatory response during MIRI in a rat model by reducing the expressions of TNF-α, IL-18, IL-1β, and high-mobility group box 1 protein (HMGB1) [19].

Senkyunolid-H inhibited the NF-κB signaling pathway to inhibit the expression of TNF-α in mice and cell models of CIRI [34].

In rat and cell models of MIRI, emodin inhibited inflammatory response by suppressing the inflammasome pathway of TLR4/MyD88/NF-κB/NLRP3, as evidenced by a reduction in the IL-1β level [40].

In mice and cell models of MIRI, gastrodian inhibited the inflammatory response by suppressing the NLRP3/caspase-1 inflammasome

pathway, as evidenced by a reduced IL-1β level [42].

In rat and cell models of CIRI, hydroxysafflor yellow A decreased activation of the NF-κB signaling pathway and inhibited the levels of NLRP3, ASC, caspase-1, IL-1β, and IL-18 to alleviate inflammation after injury [43].

Procyanidins are flavonoid polyphenols extracted from grape seeds. Procyanidins exhibit neuroprotective activity against CIRI in rat and cell models by inhibiting the TLR4-NF-κB-NLRP3 inflammasome signaling pathway and reducing the levels of caspase-1 and IL-1β [49].

Oleanolic acid inhibited the inflammatory response in a rat model of RIRI by increasing the IL-10 level and decreasing the Interferon-γ (IFN-γ), IL-6, and myeloperoxidase (MPO) levels [45].

Magnolol inhibited the inflammatory response during RIRI in a rat model by reducing the TNF-α, IL-1β, and IL-6 levels and increasing the IL-10 level [46].

Promotion of damaged histocyte proliferation

In mice and cell models of MIRI, tanshinone IIA activated the SIRT1/PGC-1α signaling pathway to maintain mitochondrial homeostasis, thereby activating the pro-proliferative capacity of cardiac microvascular endothelial cells [22].

Astragaloside VI is natural saponin that is abundant in *Radix Astragali*. In rat and cell models of CIRI, astragaloside VI promoted the proliferation and neurogenesis of neural stem cells and improved nerve function repair by activating the epidermal growth factor receptor-mediated MAPK/ERK signaling pathway [50].

Ilexonin A is a Chinese herbal medicine extracted from *Ilex pubescens*. In a rat model of CIRI, ilexonin A could promote revascularization and neuronal regeneration and regulated glial cell activation, providing a favorable microenvironment for neural recovery [51].

Conclusion and prospects

In this paper, 31 CHMs were mapped according to their mechanisms of action. **Figures 1** and **2** shows the CHMs that act to protection damaged cells, while **Figures 3** and **4** shows those that inhibit inflammatory cells. In the mapping process, we referred to the signaling pathways from https://www.cellsignal.cn along with the mechanisms described in the literature to determine the targets of the 31 CHMs. **Figures 1** and **2** shows the mechanisms by which CHMs intervene in apoptosis and some new forms of programmed cell death. **Figures 3** and **4** shows the mechanisms by which CHMs intervene in inflammatory response. The involved signaling pathways include PI3K/Akt, JAK/STAT, the MAPK family, Nrf2, SIRT1, NF-κB/NLRP3, oxidative stress, ER-stress, apoptosis, pyroptosis, and others related to new forms of programmed cell death. These pathways play important roles in the regulation of ischemia-reperfusion injury by CHMs.

PI3K/Akt signaling pathway

PI3K/Akt is a classical signaling pathway in cells that plays an important role in regulating different cellular functions, including the control of metabolism, growth, proliferation, and survival [52, 53]. This signaling pathway is involved in most of the death signaling processes. Among the CHMs considered in this paper, 11 protect damaged cells by activating the PI3K/Akt signaling pathway: dihydroquercetin, platycodin D, salvianolic acid A, salvianolic acid B, astragaloside IV, baicalin, senkyunolide-H, puerarin, tanshinone I, magnolol, and apigenin.

JAK/STAT signaling pathway

The JAK/STAT signaling pathway is the main signaling mechanism for cytokines and growth factors. It mainly regulates cell growth, survival, and differentiation [54, 55]. Three of the reviewed CHMs protect against apoptosis by activating this signaling pathway: matrine, astragaloside IV, and baicalin.

MAPK family signaling pathway

The MAPK family includes p38, JNK, and ERK [56]. Among them, p38 affects a variety of intracellular responses and has a recognized role in inflammation, cell cycle regulation, apoptosis initiation, development, differentiation, senescence, and tumorigenesis [57]. Three CHMs discussed in this review protect against apoptosis by inhibiting this signaling pathway:

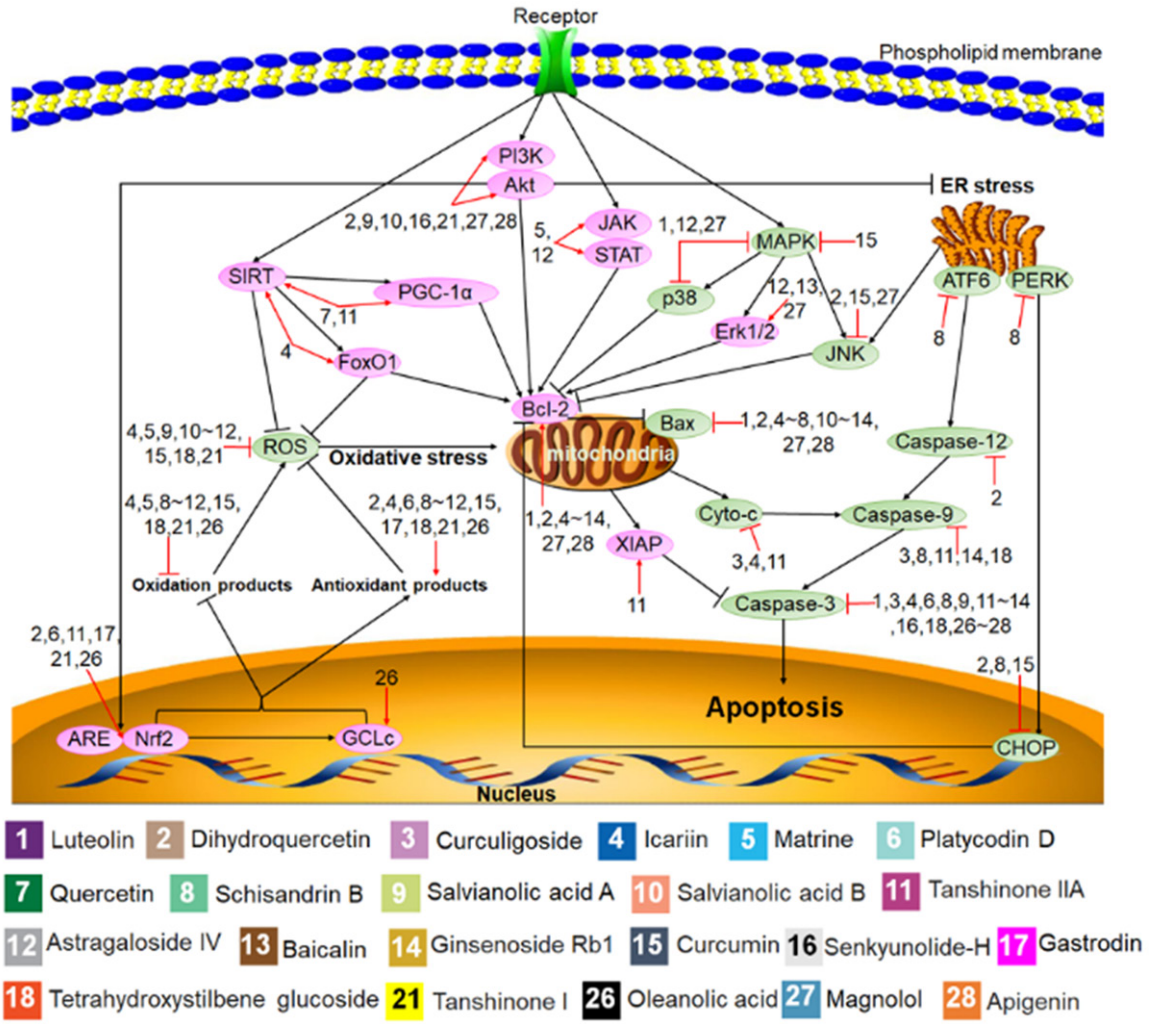

Figure 1. Protective mechanisms of Chinese herbal monomers (CHMs) in histocytes against apoptosis. The black lines represent the signaling pathways, the red lines represent the effect of the CHMs on the signaling pathways, and the pink and green ovals represent the cell signaling molecules activated and inhibited by the CHMs. Numbers represent each type of CHMs.

luteolin, astragaloside IV, and magnolol. JNK plays an important role in a variety of physiologic and pathologic processes, including the cell cycle, reproduction, cellular stress, and apoptosis [58, 59]. Three of the reviewed CHMs protect against apoptosis by inhibiting the JNK signaling pathway: dihydroquercetin, curcumin, and magnolol. ERK plays an important role in mediating cell survival, growth, proliferation, and migration [60]. Interestingly, astragaloside IV, baicalin, and magnolol activate the ERK signaling pathway during anti-apoptosis, whereas curcumin inhibit this signaling pathway in anti-apoptosis. These differences may result from interactions among several signaling pathways.

Nrf2 signaling pathway

Nrf2 is a key transcription factor that regulates resistance to oxidative stress, and the Nrf2 signaling pathway plays an important role in inducing antioxidant response in the body [61]. The primary transcriptional regulation of Nrf2 induces the expression of various antioxidant enzymes through binding associated with the ARE, GCLc transcription factor. Thus, the Nrf2 signaling pathway is important for preventing ROS damage [62]. Six of the CHMs in this review inhibit oxidative stress by activating the Nrf2 signaling pathway: dihydroquercetin, platycodin D, tanshinone IIA, gastrodin, tanshinones I, and oleanolic acid.

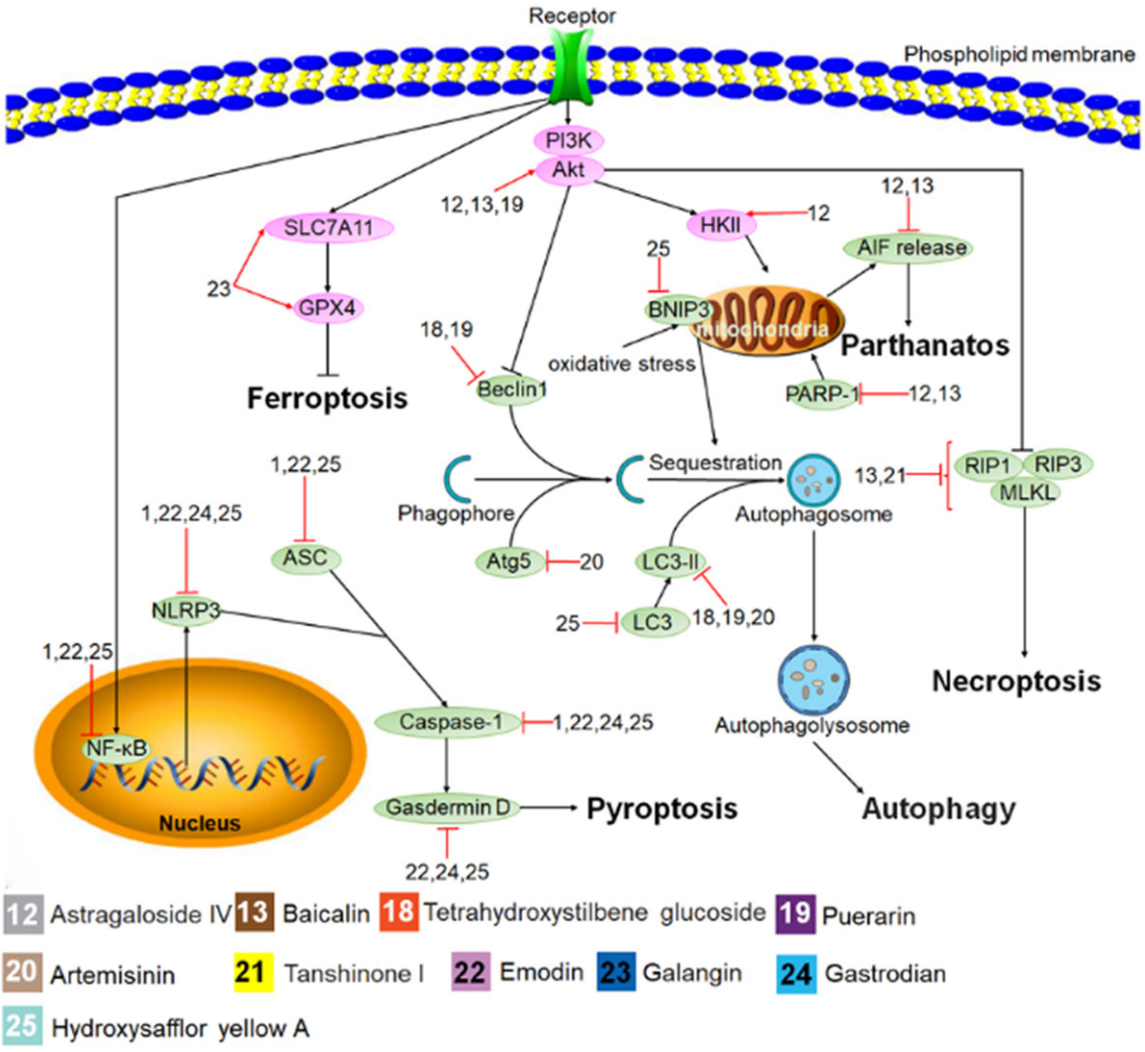

Figure 2. Protective mechanisms of Chinese herbal monomers (CHMs) in histocytes against some new forms of programmed cell death. The black lines represent the signaling pathways, the red lines represent the effect of the CHMs on the signaling pathways, the pink and green ovals represent the cell signaling molecules activated and inhibited by the CHMs, and numbers represent each type of CHMs.

SIRT1 signaling pathway

The SIRT1 signaling pathway plays an important role in the upregulation of antioxidants and downregulation of pro-apoptotic processes in the body as an aging-relieving, lifespan-extending, and metabolic pathway regulator [63, 64]. Three CHMs discussed in this review protect cells against oxidation and apoptosis by activating the SIRT1 signaling pathway: icariin, quercetin, and tanshinones IIA.

NF-κB/NLRP3 signaling pathway

The NF-κB/NLRP3 signaling pathway regulates a range of genes involved in cellular physiological activities such as innate and adaptive immunity, inflammation, stress response, B-cell development, and lymphoid organogenesis. This pathway is mediated by gasdermin D, which causes pyroptosis [65]. Three CHMs in this review protect cells against inflammatory response by inhibiting the NF-κB/NLRP3 signaling pathway, while four CHMs protect cells against pyroptosis by inhibiting this signaling pathway.

Oxidative stress and ER stress signaling pathway

Oxidative stress describes an imbalance of ROS and free radicals, leading to harmful

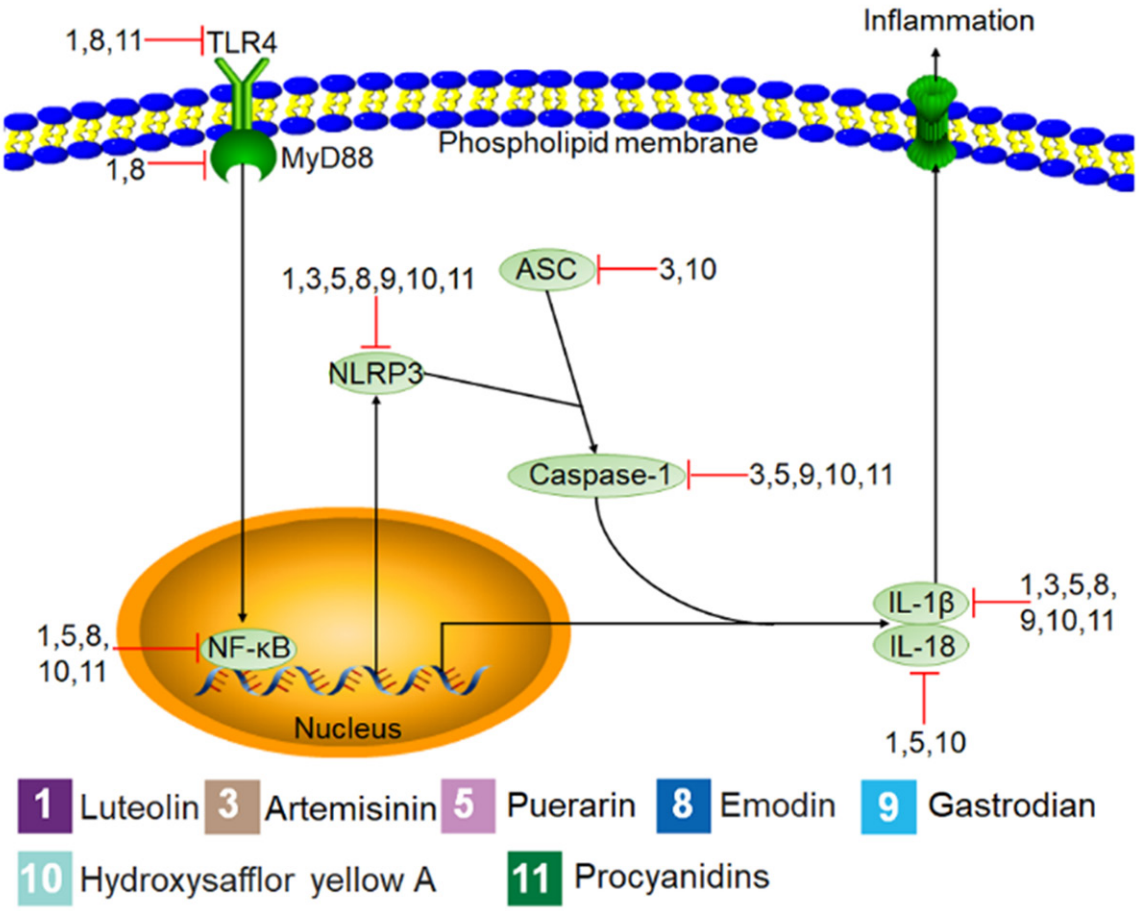

Figure 3. Mechanisms of Chinese herbal monomers (CHMs) inhibition in inflammatory cells. The black lines represent the signaling pathways, the red lines represent the effect of the CHMs on the signaling pathways, the pink and green ovals represent the cell signaling molecules activated and inhibited by the CHMs, and numbers represent each type of CHMs.

effects in the body. ROS are the main factor contributing to oxidative stress. Oxidative stress can induce apoptosis and others forms of programmed cell death [66]. ER stress is induced by caspase-12-mediated apoptosis through activation of the ATF6 pathway, and activation of the PERK and JNK pathways induces mitochondrial damage to cause apoptosis [11].

Apoptosis signaling pathway

Apoptosis is a strictly controlled mode of cellular death characterized by nuclear sequestration, cellular crumpling, cell membrane blistering, and DNA fragmentation [67]. Apoptosis is characterized by the translocation of the death signal transduction by cellular receptors through the above signaling pathways as well as the oxidative stress and ER-stress pathways to the mitochondria, which act as the central focus for the release of anti-apoptotic molecules Bcl-2, pro-apoptotic molecules Bax, cyto-c, and caspases as a family of cysteine proteases that become the central regulatory molecules of apoptosis [68].

Pyroptosis signaling pathway

Pyroptosis, also known as cellular inflammatory necrosis, is manifested by the continuous swelling of cells until the cell membrane ruptures, leading to the release of cellular contents, which activates a strong inflammatory response [69]. Pyroptosis is characterized by the transduction of death signals from the NF-κB/NLRP3 signaling pathway to the nucleus through cellular receptors. This is followed by

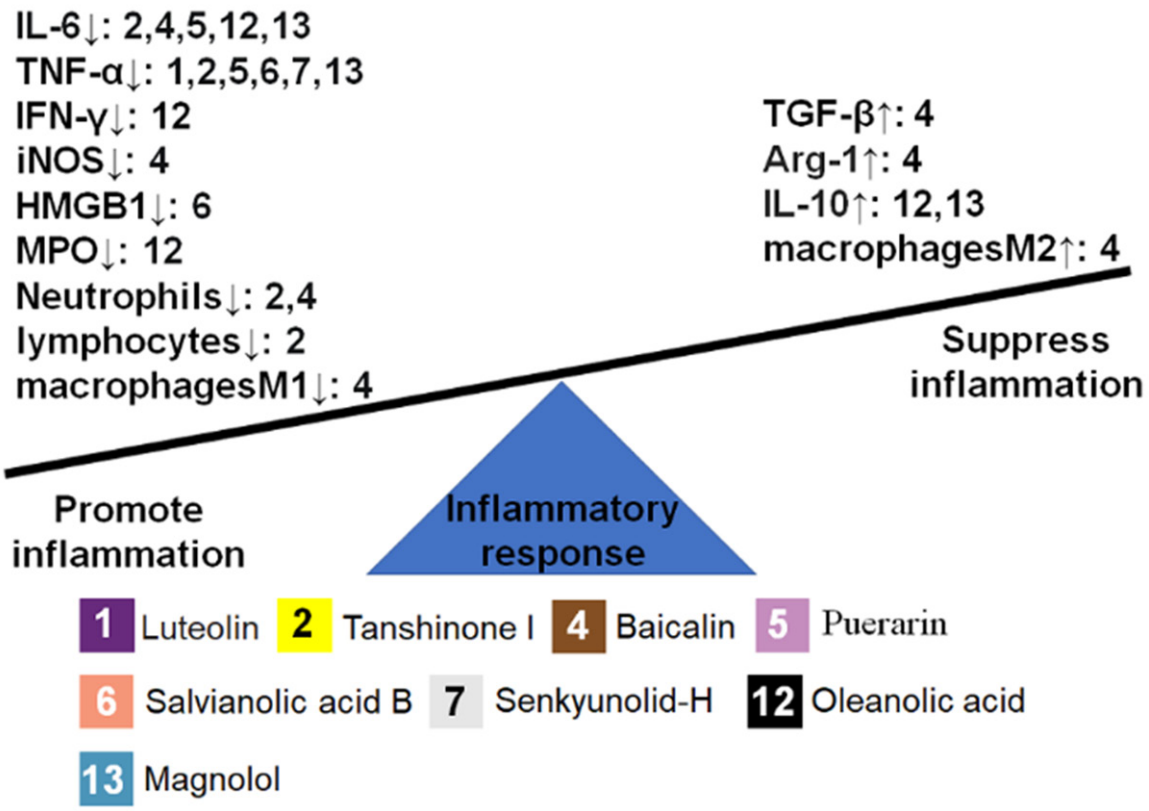

Figure 4. Chinese herbal monomers (CHMs) with effects on cytokines and inflammatory cells. The left and right sides of the seesaw represent the promotion and inhibition of inflammation, the arrows up and down represent promotion and inhibition of cytokines and inflammatory cells, and numbers represent each type of CHMs.

the activation of the NLRP3 inflammatory complex, recruitment and activation of caspase-1, and ultimately gasdermin-mediated programmed cellular necrosis accompanied by a massive release of pro-inflammatory factors [70].

Signaling pathways for new forms of programmed cell death

Autophagy, a catalytic process, leads to the autophagic lysosomal degradation of major cell plasma contents, the aggregation of abnormal proteins, and excess or damaged organelles [71]. Necroptosis is caused by significant chemical or physical injury. The typical endpoints of necrosis include swelling and rupture of necrotic cells. RIP1, RIP3, and MLKL are the main molecules involved in necroptosis [72]. Ferroptosis is a non-apoptotic form of cell death that depends on the accumulation of intracellular iron, leading to elevated levels of toxic lipid peroxides [73]. Galangin can inhibit ferroptosis by activating the SLC7A11/GPX4 signaling pathway. Parthanatos, a new form of programmed cell death that involves DNA fragmentation, mitochondrial malfunction, and cell death, is caused by the activation of PARP-1 and HK-II, leading to the release of AIF from the mitochondria to the nucleus [7]. Although other inflammatory substances have been detected and quantified, the associated signaling pathways have not been elucidated. Therefore, we only summarized the pro-inflammatory and anti-inflammatory targets of CHMs acting on inflammatory substances.

We have summarized the targets of 31 CHMs in ischemia-reperfusion injury: 28 CHMs protect against histocyte damage; 13 CHMs inhibit inflammatory cells; and three CHMs promote the proliferation of damaged histocytes. CHMs show promise for the treatment of ischemia-reperfusion injury. Existing treatment experiences for ischemia-reperfusion injury can be used as a reference.

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Disclosure of conflict of interest

None.

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