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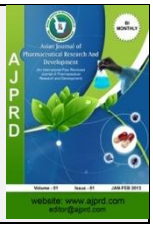

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Review Article

The Role of Ginsenosides in Myocardial Ischemic Injury-A Systematic Review

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A B S T R A C T

Ischemic heart disease (IHD) is one of the leading causes of death and disability worldwide and its incidence is increasing year by year. The effective strategy of clinical treatment for reducing myocardial infarction area and ischemic injury is to restore blood flow as soon as possible. However, the recovery of the blocked-coronary circulation may lead to myocardial reperfusion injury. At present, many evidence haveshownthat myocardial ischemia-reperfusion injury (MIRI) was related to inflammation, apoptosis, and oxidative stress. Therefore, it is urgent to find a way to prevent myocardial ischemia or to reduce the degree of reperfusion injury. Panax ginseng C. A. Meyer (ginseng) is a famous Chinese herbal medicine. Ginsenosides are the main active ingredients of ginseng. Ginsenosides have extensive pharmacological activities, such as the properties ofantioxidant, anti-inflammation, anti-apoptosis, anticancer, and so on. Ginsenosides have potential cardiovascular benefits and have been shown to improve cardiac function in animal models and humans. Therefore, in this review, we summarize various mechanisms of action of ginsenosides and reveals that ginsenosides can improve the effect of MIRI through various ways, providing reference and suggestions for further research in this field.

Keywords: Ginsenoside, Myocardial ischemia, Antioxidant, Anti-inflammation, Anti-apoptosis

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INTRODUCTION

Myocardial ischemia is a pathological process reducing blood supply of the heart, which leads to a decrease of oxygen of myocardial cells and an abnormal energy metabolism of the heart. Myocardial ischemia can result in an irreversible injury of heart tissues. It had been proved that ischemic myocardium could be saved from infarction by blood reperfusion in dogs[1]. Since then, reperfusion was conducted in patients with acute myocardial infarction, using drug thrombolysis or catheter to reopen the occluded coronary arteries[2]. Now, the effective strategy for rescuing myocardial cells from myocardial infarction is timely reperfusion. However, reperfusion may lead to myocardial ischemia-reperfusion injury (MIRI), resulting in heart tissue injury and destruction. In the past time, researchers have made a progress in elucidating the mechanism of MIRI and found many strategies and methods to make myocardial cells more resistant to ischemia. However, the exact mechanism of MIRI remains unknown.

MIRI is related to multiple factors. Necrosis will take place during myocardial ischemia. Necrosis is characterized by swelling of cells, nucleus karyolysis, disrupted plasma membrane, adjacent inflammation. This morphological

change of myocardial cells is due to the influx of extracellular ions and fluid resulting from an early loss of plasma membrane integrity. Myocardial cells apoptosis occurs during or after myocardial ischemia-reperfusion[3]. The apoptotic cells are often found in the hypoxia zone of myocardium. The morphology of apoptotic cells is the contraction of myocardial cells and their nuclei. Unlike necrotic cells, the plasma membrane of apoptotic cells will be intact until the late apoptotic process[4]. If myocardial ischemia persists, irreversible injury and necrosis ensue. Reactive oxygen species (ROS, e.g., superoxides, peroxides, or free radicals) accumulate in myocardial cells. ROS play an important role in the process of cell death induced by MIRI. ROS, mainly produced by activated neutrophils, act as a mediator of cell death triggered by other enzymes[5-6]. In the early stage of reperfusion, the activated-neutrophils are recruited from blood into the myocardium by pro-inflammatory substances (e.g., TNF-α, IL-6, platelet activation factor, complement, LTB4)[7]. This phenomenon suggests that inflammatory responses may initiate during reperfusion, which leads to a cascade of reactions and results in MIRI.

Recently, early reperfusion therapy with either administration of fibrinolytic agents or primary percutaneous coronary intervention is recommended for patients presenting myocardial ischemia. However, reperfusion therapy will induce metabolic dysfunction of myocardial cells and even irreversible injury of myocardium. Up to date, MIRI has become the main obstacle of obtaining the best efficacy from reperfusion therapy. MIRI also affects the prognosis and augments the follow-up cost of patients with myocardial ischemia. Now, numerous cardioprotective strategies have been conducted to attenuate MIRI. Although preclinical studies have shown promising results in counteracting MIRI, these strategies still did not achieve success in clinical use[2]. Therefore, it remains an urgent need to find a novel approach that can reduce MIRI and improve mortality and morbidity in MIRI patients.

The pathologic process of MIRI is involved in multiple factors. Recent reports suggested that Traditional Chinese Medicine (TCM) may be promising agents for ameliorating MIRI and attracts attentions of researchers. *Panax ginseng* C. A. Meyer (ginseng) is a famous herbal medicine. In China, ginseng has been used to treat various diseases for thousands of years. Ginseng contains a variety of active ingredients and the major bioactive ingredients are ginsenosides[8-10]. Ginsenosides are classified into three main structural types: glycosides of protopanaxadiol (PPD-type ginsenosides), glycosides of protopanaxatriol (PPT-type ginsenosides), and oleanane-type ginsenosides[8]. Now, more and more ginsenosides are being identified. Widely studied ginsenosides include Rb1, Rb2, Rc, Rd, Rg1, Rg2, Rg3, Re, Rf, Rh1 and Rh2[8-10]. Current evidence shows that ginsenosides have cardioprotective effects against MIRI through anti-oxidation, anti-inflammation, and anti-apoptosis[11-14]. Therefore, this review summarizes the mechanism of myocardial ischemia-reperfusion injury caused by inflammation, apoptosis and oxidative stress, and the mechanism of ginsenosides improving reperfusion injury through some ways.

Myocardial ischemia-Reperfusion injury

Myocardial cell death occurs during ischemia, leading to myocardial infarction[15]. Myocardial infarction is the most serious outcome of coronary artery disease. To avoid myocardial infarction, restoring the blood supply of ischemic myocardium is needed. However, reperfusion may cause ventricular arrhythmias, reversible systolic impairment, and microvascular dysfunction[14]. Multiple researches confirmed the existence of MIRI. Myocardium injury during myocardial reperfusion results in four types of cardiac dysfunction: myocardial shock, reperfusion arrhythmias, no-reflow phenomenon, lethal reperfusion injury. Several processes have been found to play a key role in MIRI: oxidative stress, inflammation, calcium paradox, Ph paradox, mitochondrial disorders, etc.[16].

The formation process of MIRI is complex and involves multiple pathological processes. During prolonged ischemia, anaerobic metabolism and lactic acid accumulation inevitably occur, leading to a decrease in ATP level and intracellular pH. As a result, ATPase-dependent ion transport mechanisms become dysfunctional, leading to increased intracellular and mitochondrial calcium levels (calcium overload), cell swelling and rupture, and cell death through necrosis, apoptosis, and autophagy. Although oxygen levels recovered after reperfusion, the production of reactive oxygen species surged, and pro-inflammatory neutrophils infiltrated ischemic tissue, exacerbating ischemic injury[17]. Therefore, researchers should focus on oxidative stress, mitochondrial damage, inflammation, calcium overload, apoptosis and other aspects in the treatment of MIRI and search for therapeutic targets, instead of only focusing on a single mediator.

Reactive oxygen species (ROS)are free radicals. ROS have an unpaired electron in the outer orbital. ROS have the potential to steal hydrogen atoms and therefore forms abnormal molecular bonds. The molecules of cells that react with ROS are in turn converted to free radicals, continuing the destructive cascade of cells. Overproduction of ROS damages cell membranes, denatures proteins, and even disrupts cell chromosomes[18]. Furthermore, ROS are also linked to the initiation of the inflammatory cascade. Numerous data have shown that ROS play key roles in the pathological injury of cardiovascular diseases[19-20]. Myocardial ischemia leads to the increase of ROS, especially at the time of reperfusion[21]. Studies have found that there are a variety of potential sources of ROS during myocardial ischemia-reperfusion. Mitochondria of myocardial cells are the main source of ROS production during reperfusion[22]. Mitochondrial dysfunction plays a cardinal role of MIRI[23].

Myocardial ischemia causes cellular injury and death and then initiates a pro-inflammatory response[24]. Myocardial ischemia-induced damage-associated molecular patterns results in the release of pro-inflammatory mediators, including cytokines and chemokines, which lead to the recruitment of inflammatory cells into the ischemic myocardium, and augment the inflammatory response following myocardial ischemia-reperfusion[25-26]. Infiltration of inflammatory cells may cause the death of cardiomyocytes, thereby extending ischemic injury beyond

the original myocardial ischemia zone[27]. The inflammatory response induced by MIRI plays an important role in determining the degree of myocardial injury and subsequent myocardial remodeling. Anti-inflammation is a potential therapeutic strategy for improving clinical outcomes in myocardial ischemia patients.

Classification of Ginsenosides

Panax ginseng C. A. Meyer (ginseng) is a famous Chinese herbal medicine. Ginseng has been worldwide used in oriental countries for thousands of years to prevent or treat diseases. In China, Japan, and Korea, ginseng has been widely used to prevent aging or replenish physical strength. It was reported that ginseng showed pharmacological effects in the cardiovascular, nervous, endocrine, and immune systems. Ginseng can improve blood flow and protect cardiovascular function[27]. Ginsenosides have the properties to ameliorate a variety of pathological factors and maintain the body homeostasis. Ginsenosides have potential cardiovascular benefits, including antioxidative and anti-inflammatory, or anti-apoptotic effects.

Ginsenosides are the main active constituents of ginseng. Ginsenosides are classified into three major groups (Table 1), including dammarane-type tetracyclic triterpenoid saponins (PPD, ginsenoside Ra1, Ra2, Ra3, Rb1, Rb2, Rb3, Rc, Rd, Rg3, Rh2, Rs1, Rs2, etc.), dammarane-type tetracyclic triterpenoid saponins (PPT, ginsenoside Re, Rf, Rg1, Rg2, Rh1, Rh3, Rf1, etc.), and oleanolic acid type pentacyclic triterpenoid saponin (OA, ginsenoside Ro).

Table 1: Classification of ginsenosides

Subtype	Ginsenosides
Dammarane-type tetracyclic triterpenoid saponins, PPD	Rb1, Rb2, Rb3
	Rg3
	Rc
	Rd
	Ra1, Ra2, Ra
	Rh2
	Rs1, Rs2
dammarane-type tetracyclic triterpenoid saponins, PPT	Rh1
	Rg1, Rg 2
	Re
	Rf
	Rh 3
Oleanolic acid, OA	Ro

The Effects of Ginsenosides on Myocardial Ischemia-Reperfusion Injury

Inflammation, oxidative stress, and apoptosis play important roles in the pathophysiological process of MIRI. Previous studies demonstrated that ginsenosides alleviated MIRI by regulating oxidative stress, inflammation, or apoptosis[28]. Ginsenosides had effective antioxidant activities[29]. The productions of pro-inflammatory cytokines, chemokines, and adhesion substances after MIRI cause inflammatory responses. Ginsenosides showed a property of inhibiting the inflammation and apoptosis[30-31].Therefore, it is a promising research idea to explore the new mechanism of ginsenosides in the treatment of myocardial ischemia-reperfusion injury through anti-inflammatory, antioxidant, anti-apoptotic and other pathways[32].

PPD

PPD includes a variety of ginsenosides. Recent works focus on studying the pharmacological effects of ginsenosides Rb1, Rb2, Rb3, Rg3, Rc, and Rd. Mechanisms andsignallingpathways of PPD against myocardial ischemia were summarized (Table 2).

Table 2: Mechanisms and signaling pathways of PPD against myocardial ischemia

Ginsenosides	Pharmacological actions	Signaling pathways
Rb1	Anti-inflammation, anti-oxidation, anti-apoptosis	Mitochondrial complex I, TNF-α, IL-6, mTOR
Rb2	Anti-inflammation, anti-oxidation, anti-apoptosis	SIRT1
Rb3	Anti-inflammation, anti-oxidation, anti-apoptosis	PERK/Nrf2/HMOX1
Rg3	Anti-inflammation, anti-apoptosis	P53, SIRT1/NF-κ B, Bcl-2, Bax, FoxO3a
Rc	Anti-oxidation	SIRT1/PGC1α
Rd	Anti-oxidation, calcium channel blocker	Akt/GSK-3B

Ginsenoside Rb1

There is relatively high quantity of ginsenoside Rb1 in ginseng[33]. The chemical structure of ginsenoside Rb1 is shown in Figure 1A. Studies have shown that the protective effect of Rb1 on MIRI may be related to the regulation of mitochondrial complex I,TNF-α, IL-6, mTOR pathway.

During myocardial ischemia-reperfusion, a series of reactions, such as the disorder of energy metabolism, disruption of redox reaction, and accumulation of ROS, occur. Therefore, antioxidant or inhibiting ROS generation are a promising strategy for the treatment of MIRI. It has been demonstrated that the citric acid cycle intermediate succinic acid accumulates significantly in cardiomyocytes during ischemia. After reperfusion, the accumulated succinic acid acts as a reducing equivalent to drive mitochondrial complex I to produce superoxide by a reverse electron transfer (RET) reaction. Due to the large production of superoxide in mitochondrial complex I, blocking electron transport at this time may reduce ret-mediated ROS production and protect the heart from I/R damage. Then, the search for a compound that reversibly inhibits mitochondrial complex I to treat reperfusion injury is promising to be clinically realized. C57BL/6J mice were subjected to blocking left anterior descending coronary artery and followed by reperfusion for 15 min, 24 h, 14 days, or 28 days. Treatment with ginsenoside Rb1 at dose of 50 mg/kg attenuated MIRI, and the mechanism was associated with ginsenoside Rb1 binding to mitochondrial complex I and then inhibiting mitochondrial complex I-mediated ROS production[34]. It is well known that diabetes mellitus, hyperlipidemia, and oxidative stress are common risk factors for myocardial ischemia. Db/db mice were treated with ginsenoside Rb1 at dose of 25, 50 and 100 mg/kg for 12 weeks. The results showed that ginsenoside Rb1 attenuated the levels of CRP, MCP-1, IL-1β, IL-6, and TNF-α in serum. This work demonstrated that ginsenoside Rb1 ameliorated MIRI of diabetic animals by regulating adipocytokine pathway and antioxidant pathway[35]. The left coronary artery of SD rats was occluded for 45 min followed by reperfusion for 2 h. Ginsenoside Rb1 showed a protective effect against MIRI. Ginsenoside Rb1 not only down-regulated the expressions of Bax, Bcl-2, and cleaved caspase3 but also activated the phosphorylation of mTOR[36]. In C57BL/6 mice, ginsenoside Rb1 ameliorated diabetes-induced cardiac dysfunction and abnormal calcium signaling pathway of cardiomyocyte. Ginsenoside Rb1 also reduced calcium leakage and increased calcium uptake[37].

Ginsenoside Rb2 and ginsenoside Rb3

Ginsenoside Rb2 (Figure 1B) and its isoform ginsenoside Rb3 (Figure 1C) had been demonstrated to have a protective effect on MIRI. The combination of ginsenoside Rb2 and ginsenoside Rb3 had similar protective effects on MIRI as ginsenoside Rb3. The myocardial ischemia-reperfusionrat model was treated with ginsenoside Rb3/Rb2 (20 mg/kg) or ginsenoside Rb3 (20 mg/kg) alone, once a day for 3 consecutive days. Ginsenoside Rb3/Rb2 attenuated MIRI, improved cardiac function, reduced myocardial ischemic area, and decreased activities of aspartate aminotransferase, lactate dehydrogenase, and CK-MB. Ginsenoside Rb3/Rb2 decreased levels of IL-6 and TNF-α, and malondialdehyde content, and augmented the activities of superoxide dismutase and glutathione peroxidase. Ginsenoside Rb3/Rb2 decreased the expression of caspase-3, Bcl-2, and Bax. Ginsenoside Rb2 and Rb3 exerted protective effects on MIRI through anti-inflammation, anti-oxidation, and anti-apoptosis[38]. Recently, myocardial ischemia-reperfusionrats were orally administered with ginsenoside Rb3 for 5 days. Ginsenoside Rb3 elevated the total antioxidant level through activating PERK/Nrf2/HMOX1 signaling pathway, and exerted protective effects on myocardial infarction and heart failure[39]. Ginsenoside Rb3 treatment also reduced infarct size in myocardial ischemia-reperfusion rats. The mechanism of action of ginsenoside Rb3 was related to its antioxidant activity and improvement of microcirculation[40]. In isoproterenol-induced myocardial ischemia rats, ginsenoside Rb3 attenuated myocardial injury and improved cardiac function. The cardiac protective effect of ginsenoside Rb3 was at least partly related to the antioxidant activity[41]. Inflammation and oxidative stress may coexist in MIRI. In the rats of coronary artery ligation, ginsenoside Rb2 reduced superoxide production and the levels of IL-1β, IL-6, and TNF-α. These findings demonstrated that ginsenoside Rb2 could inhibit the oxidative stress and inflammation induced by MIRI. Previous study reported that ginsenoside Rb2 up-regulated SIRT1 expression and down-regulated p53 expression. However, SIRT1 inhibitor, EX527, offset the protective effect of ginsenoside Rb2, indicating that the pharmacological action of ginsenoside Rb2 is associated with SIRT1 signaling pathway[42]. In oxygen and glucose deprivation reperfusion-induced H9c2 cells, ginsenoside Rb3 attenuated the apoptosis of H9c2 cells by inhibiting ROS production. The mechanism was related to the inhibition of NF-κB signaling pathway by ginsenoside Rb3[43]. Ginsenoside Rb3 also showed an improvement in heart failure caused by MIRI. GinsenosideRb3 up-regulated the expression of enzymes which were involved in fatty acid β-oxidation, including carnitine palmitoyl transesterase-1α, acyl-CoA dehydrogenase long-chain enzyme, and sirtuin 3 (SIRT3)[44].

Ginsenoside Rg3

Previous study showed that ginsenoside Rg3 (Figure 1D) had cardioprotective effect on MIRI[45]. Ginsenoside Rg3 with ROS-responsive nanoparticle can release ginsenoside Rg3 when it meets ROS at the location of myocardial ischemia-reperfusion.Then, ginsenoside Rg3 activated FoxO3a signaling pathway and inhibited oxidative stress, inflammation, and apoptosis[46]. Ginsenoside Rg3 attenuated angiotensin II-induced cardiac hypertrophy and fibrosis in a dose-dependent manner. In addition, ginsenoside Rg3 inhibited NLRP3-ASC-caspase 1 inflammasome and ROS production in Ang II-challenged cardiomyocytes. The mechanism of action of ginsenoside Rg3 was related to regulating SIRT1/NF-κB pathway and inhibiting NLRP3 inflammasome and oxidative stress[47]. Ginsenoside Rg3 was administered at dose of 5 or 20 mg/kg, once daily for 7 days. Ginsenoside Rg3 improved the cardiac function in myocardial ischemia-reperfusion rats. It was also reported that ginsenoside Rg3 displayed anti-apoptotic and anti-inflammatory properties in myocardial ischemia-reperfusion animal model[48].

Ginsenoside Rc

Myocardial ischemia model was induced by isoproterenol in Swiss mice. Ginsenoside Rc (Figure 1E) (10, 20, 40 mg/kg) treatment decreased the levels of CK-MB and troponin T. Ginsenoside Rc attenuated myocardial necrosis and inflammatory cell infiltration. Ginsenoside Rc not only decreased the content of MDA and TNF-α, but also augmented the content of GSH in myocardial tissue. Ginsenoside Rc also increased the expressions of Nrf2, GCLC, GCLM, and HO-1. Nrf2 inhibitor, ML385, offset ginsenoside Rc-mediated cardiac protection. The pharmacological action of ginsenoside Rc is related to its antioxidant and anti-inflammatory effects[49]. Energy metabolism is the core and most important function of metabolizing active tissues such as the heart and brain. Glucose aerobic metabolism plays a potential role in ATP production and maintains multiple biochemical processes in cardiomyocytes and neurons. Epidemiological, clinical, and experimental evidence strongly supports that bioenergetic impairment typically occurs in myocardial and cerebral ischemic disorders followed by reperfusion injury. There is no doubt that enhancing energy metabolism has been a potential strategy to improve physical endurance and reduce pathological damage to protect heart and neuronal function. Ginsenoside Rc is a SIRT1 activator and it increased glucose uptake, pyruvate metabolism, and mitochondrial biosynthesis in myocardial tissues, we boldly speculate that ginsenosides are a potential candidate for the treatment of myocardial ischemia-reperfusion.[50]. These properties mentioned above may be useful for the prevention and treatment of MIRI.

Ginsenoside Rd

Ginsenoside Rd(Figure 1F) has a variety of pharmacological activities, such as anti-oxidation, anti-apoptosis, and anti-inflammation[51]. Rats were subjected to myocardial ischemia- reperfusion, and they were treated with ginsenoside Rd at dose of 50 mg/kg. Ginsenoside Rd elicited a cardioprotective effect on MIRI. The mechanism was related to decreasing intracellular ROS production and inhibiting mitochondrial apoptosis, and regulating Akt/GSK-3β signaling pathway[52]. Calcium overload plays an important role in the pathophysiological processes of MIRI. It was reported that ginsenoside Rd had the property of blocking calcium channels through acting on Gi protein and NO/cGMP signaling pathway, and therefore ameliorated MIRI[53].

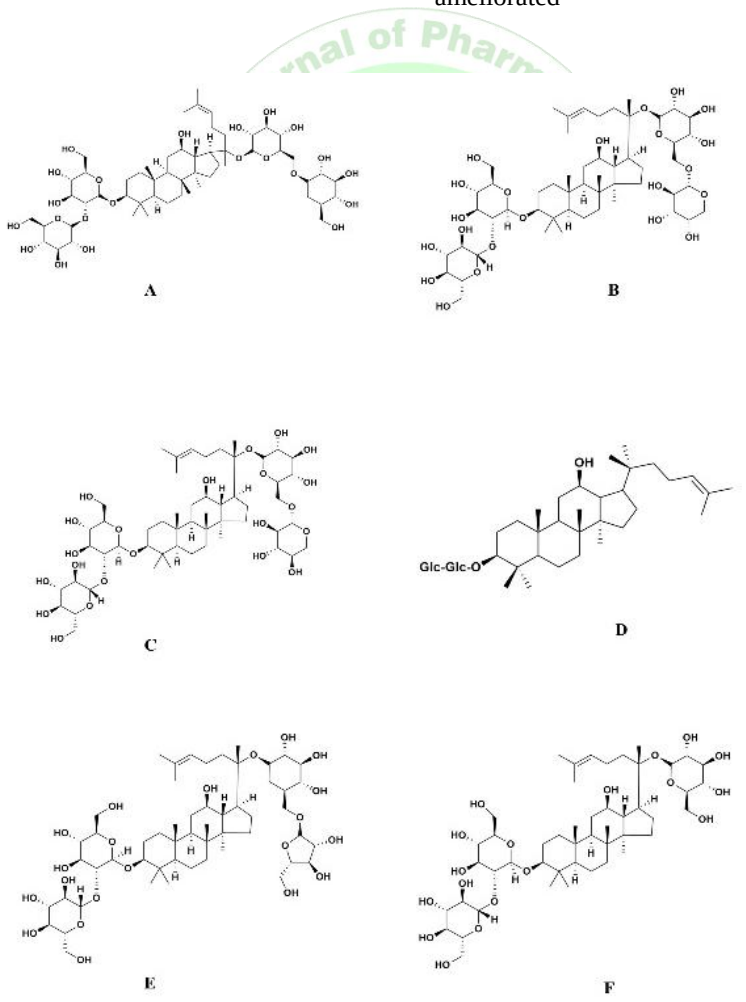

Figure 1: Chemical structure formula of some PPD ginsenosides. (A). Ginsenoside Rb1. (B). Ginsenoside Rb2. (C). Ginsenoside Rb3. (D). Ginsenoside Rg3. (E). Ginsenoside Rc. (F). Ginsenoside Rd.

PPT

PPT mainly including ginsenoside Re, Rf, Rg1, Rg2, Rh1, and Rh3 are the major bioactive ingredients of ginseng. Recent works of PPT focused on studying the effects of ginsenoside Re, Rf, Rg1, Rg2, Rh1, and Rh3 on cancer, neurological diseases, and cardiovascular diseases. There were studies which reported that PPT showed a protective effect on MIRI. Mechanisms and signaling pathways of PPD against myocardial ischemia were summarizedin Table 3.

Table 3: Mechanisms and signaling pathways of PPD against myocardial ischemia

Ginsenosides	Treatment mechanisms	Action pathways
Rh1	Anti - inflammation, anti - oxidation	SOD and TNF-α
Rg1	Regulation of energy metabolism	ATP5D, RhoA/ROCK
Rg2	Anti – inflammation, anti - oxidation	SIRT1, TAK1
Re	Anti – inflammation	TNF-α, HIF-1α

Ginsenoside Rh1

Ginsenoside Rh1 (Figure 2A) had been reported to have pharmacological effects including anti-inflammation, anti-oxidation, immunomodulation, and so on. These activities of ginsenoside Rh1 partly elucidated the beneficial effects of ginseng on reducing cardiovascular risk factors . Rats were subcutaneously injected with isoproterenol at dose of 20 mg/kg to induce myocardial infarction. The rats were administered with ginsenoside Rh1 for 7 consecutive days. Ginsenoside Rh1 reduced the levels of serum creatine kinase-MB and troponin T, suggesting that ginsenoside Rh1 attenuated myocardial injury and improved cardiac function. Further experiment indicated that the mechanism of action was related to regulating activities of SOD, catalase, and GSH-Px, and to decreasing contents of TNF-α and IL-1β (54).

Ginsenoside Rg1

Using rat cardiomyocyte, it had been demonstrated that ginsenoside Rg1 (Figure 2B) decreased LDH level and increased cell viability in a dose-dependent manner. Ginsenoside Rg1 also reduced intracellular ROS production and intracellular calcium level. The activities of SOD,catalaseand the content of GSH in cardiomyocyte were augmented when the cardiomyocytes were treated with ginsenoside Rg1. These findings suggested that the protective effect of ginsenoside Rg1 on cardiomyocytes was related to its antioxidant effect and regulation of intracellular calcium homeostasis[55]. In diabetic rats, 12-week administration of ginsenoside Rg1 decreased levels of CK-MB and troponin I, and ameliorated myocardial injury. Ginsenoside Rg1 elevated the activities of SOD, catalase, and glutathione peroxidase. Therefore, ginsenoside Rg1 had a property of decreasing oxidative stress and inhibiting apoptosis in diabetic rats. Ginsenoside Rg1 played a role in ameliorating MIRI, which is manifested in the regulation of energy metabolism. Metabolic disorders occurred during myocardial ischemia-reperfusion. Protecting mitochondria and improving energy deficiency during myocardial ischemia-reperfusion are promising approaches for the alleviating MIRI. Ginsenoside Rg1 regulated the expression of proteins which is associated with energy metabolism. Ginsenoside Rg1 enhanced the activity of mitochondrial respiratory complex and the expression of ATP5D, attenuated MIRI, and improved cardiac function by regulating RhoA/ROCK signaling pathway[56]. Recently, it is proved that angiogenesis had the potential to treat myocardial ischemia. Previous study encapsulated ginsenoside Rg1 in the gelatin microspheres. Intramyocardial injection of ginsenoside Rg1 microspheres was performed in the rats of myocardial infarction. Ginsenoside Rg1 microspheres ameliorated the myocardial fibrosis and left ventricular remodeling. Ginsenoside Rg1 microspheres increased the densities of microvessels in the border zones of the myocardial infarction, restoring the myocardial perfusion and improving the heart function[57].

Ginsenoside Rg2

Ginsenoside Rg2 (Figure 2C) is a main active compound in the root, stem, and leaf of ginseng. Rats were subjected to anterior descending coronary artery ligation and reperfusion. Ginsenoside Rg2 exerted a protective effect on MIRI. The mechanism of action is mainly involved in activating SIRT1 and attenuating oxidative stress and inflammation, the Silent Information Regulator (SIRT)1 is a histone deacetylase whose activity depends on nicotinamide adenine dinucleotide (NAD^+). SIRT1 regulates acetylated p53, thereby inhibiting apoptosis in cardiomyocytes. Activation of SIRT1 signaling prevents myocardial reperfusion damage[58]. Necrosis is the major pathway of cell death in myocardial ischemia. *In vivo* experiment showed that ginsenoside Rg2 ameliorated MIRI-induced myocardial cell necrosis. Ginsenoside Rg2 augmented the phosphorylation of TAK1, resulted in TAK1 binding to RIP1 and then blocked the formation of RIP1/RIP3 complex, attenuating MIRI[59]. These findings demonstrated that ginsenoside Rg2 is promising ingredient for the prevention and treatment of MIRI.

Ginsenoside Re

Ginsenoside Re (Figure 2D) is one of the compounds which share a relatively high content in ginseng. Ginsenoside Re is responsible for the pharmacological effects of ginsenosides. The hearts of rats were retrogradely perfused with Langendorff apparatus and then subjected to myocardial ischemia-reperfusion. Ginsenoside Re increased the recovery of heart rate, perfusion pressure, and cardiac output. Ginsenoside Re attenuated the electrocardiographic

abnormality and inhibited TNF-α production. The results indicated that ginsenoside Re had cardioprotective effects in myocardial ischemia-reperfusion[60]. *In vitro* study showed that ginsenoside Re alleviated hypoxia-reoxygenation-induced myocardial injury. The mechanism of action was related to inhibiting the interaction of HIF-1α with von Hippel-Lindau E3 ubiquitin ligase, and then inhibiting the ubiquitination of HIF-1α[61].

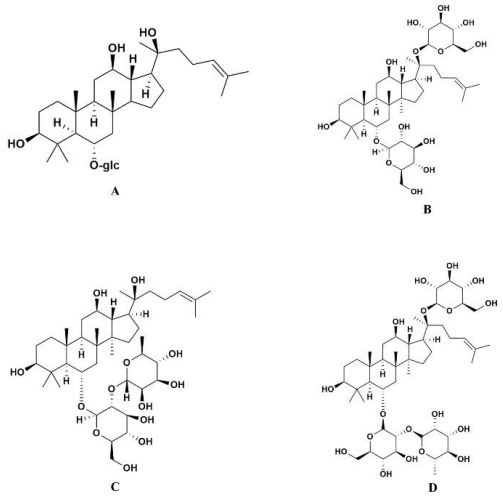

Figure 2: Chemical structure formula of PPT. (A). Ginsenoside Rh1. (B). Ginsenoside Rg1. (C). Ginsenoside Rg2. (D). Ginsenoside Re.

OA

Ginsenoside Ro (Figure 3) belongs to oleanolic acid-type ginsenoside. Previous studies demonstrated that ginsenoside Ro displayed the properties of anti-apoptosis and anti-inflammation. With rat chondrocyte, the authors found that ginsenoside Ro inhibited cells apoptosis by decreasing levels of Bax, Bad, p53 phosphorylation and increasing the expression of Bcl-xL and PCNA. Ginsenoside Ro also suppressed the expression of MMP3, MMP9, and COX-2 and inhibited NF-κB phosphorylation [62]. Ginsenoside Ro exhibited an anti-inflammatory effect in Raw 264.7 cells. The mechanism of action was involved in augmenting the expression of heme oxygenase-1 and reducing the expression of nitric oxide synthase and cyclooxygenase-2 [63]. Recent work prepared inflammation model with C57BL/6 mice and RAW264.7 macrophages. Ginsenoside Ro not only decreased the production of pro-inflammatory factors, including TNF-α, IL-6 and IL-1β but also inhibited the phosphorylation of NF-κB and mitogen-activated protein kinases. Ginsenoside Ro exerted its anti-inflammatory effect by inhibiting TLR4 signaling pathway [64]. Up to date, there are no any studies demonstrating that ginsenoside Ro plays a protective role in MIRI. But we speculate that ginsenoside Ro may have a property of alleviating MIRI through its anti-inflammatory activity.

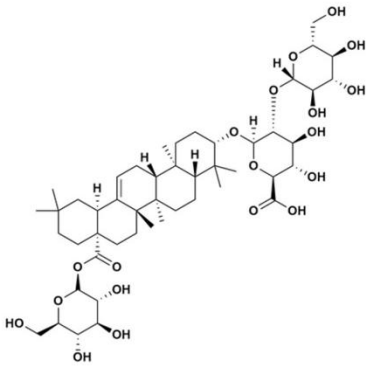

Figure 3: Chemical structure formula of OA. Ginsenoside Ro.

CONCLUSION

Currently, effective methods for preventing and treating myocardial ischemia-reperfusion remain a challenge. The cardioprotective effects of ginseng have been verified in preclinical and clinical studies. This review summarized the findings which study the effects of ginsenosides against MIRI. Mechanisms underlying the cardioprotective effects of ginsenosides are mainly associated with antioxidant, anti-inflammation, anti-apoptosis.

Although a good many of preclinical studies have been carried out to investigate the effects of ginsenosides in the treatment of myocardial ischemia, there are few clinical trials of ginsenosides found in treating myocardial ischemia. Therefore, further studies should focus on

conducting clinical trials to confirm the efficacy of ginsenosides in myocardial ischemia. Additionally, the animal models in current preclinical experiments were prepared with young rats or mice. While the patients with myocardial ischemia are more likely to be old people and to be accompanied by hypertension, hyperlipidemia, and hyperglycemia. Therefore, it is reasonable to prepare an old animal MIRI models or animal MIRI models co-existing with hypertension, hyperlipidemia, and hyperglycemia to study the cardioprotective effects of ginsenosides, which would provide a more reliable data for the clinical application of ginsenosides.

In conclusion, this review depicted the recent progresses of studies on ginsenosides in myocardial ischemia, which will help researchers understand the use of ginseng or ginsenosides for preventing and/or treating cardiovascular diseases.

Search Strategy and Selection Criteria

Data for this Review were identified by searches of PubMed and references from relevant article using the search terms “Ginsenosides”, “Myocardial ischemic Injury”, “Oxidative stress” and “Inflammation”. All influential studies were considered, regardless of the date of publication, to reflect the progress made in the role of ginsenosides in the treatment of myocardial ischemia-reperfusion injury and cardiac protection.

Author Contributions

WS,QW: conceptualizationand drafting the manuscript; WF,CZ:writing and revision; TW: supervision, review, and editing; DS:conceptualization, supervision, editing, and funding acquisition.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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