INSIGHTS INTO THE MONOMERS AND SINGLE DRUGS OF CHINESE HERBAL MEDICINE ON MYOCARDIAL PRESERVATION

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Abstract

Chinese herbal drugs have been proved to be effective agents in myocardial protection by preventing ischemia-reperfusion injury. The underlying mechanisms as to how these agents work were however poorly elucidated. Studies on the monomers or on the single drugs have highlighted the possible rationales, leading to a better understanding of the pharmaceutical effects of the active parts of the herbs. These agents have been found to be structure-sensitive while they play the role of a protective ingredient. Polysaccharides of Chinese herbal medicine have pharmaceutical effects in immune modulation, anti-inflammation, anti-virus, anti-tumor, anti-aging mechanisms, with an anti-oxidative effect being a commonly recognized mechanism. Saponins are prone to alleviate calcium overload. As bioflavonoids commonly contain active phenolic hydroxy group, they have good anti-oxidant property. Those containing effective lignanoids and essential oils can result in a reduced nitric oxide secretion of the endothelial cells and an increased intercellular cell adhesion molecule-1 expression. Alkaloids may resist free radical injuries. Most importantly, modern in-depth research revealed that myocardial infarction is typically associated with apoptosis, and herbal medicine containing carbohydrates and glycosides showed cardioprotective effects by way of inhibiting apoptosis of myocytes. As a supplement to cardioplegia, some Chinese herbal drugs have become especially valuable in myocardial protection in open heart surgery by preserving metabolic energy. In conclusion, the classification of Chinese herbal medicine made according to their main active ingredients has facilitated the expression of their functioning mechanisms. Chinese herbal drugs play an important role in cardioprotection via many different mechanisms, the most recent and important finding being the inhibition of apoptosis.

Key Words: apoptosis; Chinese herbal drugs; myocardial ischemias.

Introduction

Several theories, including calcium overload, oxygen free radicals, infiltration of granular leukocytes, complement participation, enzymatic effects, apoptosis, and gene expression disorder, *etc*., have been popularly recognized as the fundamental mechanisms of myocardial injury due to ischemia-reperfusion (Wang and He, 2004. Alternative strategies with the purpose of myocardial preservation therefore start with alleviation of calcium overload, maintenance of homeostasis of the cellular membrane, inhibition of nitric oxide (NO) delivery, and prevention of apoptosis. Recent studies discovered coagulable cytolysis around the ischemic myocardial infarction zone without presence of infiltration of inflammatory cells, a phenomenon similar to the morphological changes of apoptosis. Accordingly, an agreement was reached that myocardial infarction was typically associated with apoptosis. In a rabbit model of ischemia-reperfusion injury, scattered apoptotic cells positive for terminal deoxynucleotidyl transferase dUTP nick end-labeling were present in the ischemic region 1 hr after ischemia, peaked at 3 hrs, and decreased thereafter, whereas no apoptotic cells were found in the normal myocardium. Furthermore, apoptotic cells began to appear in the ischemic margin 1 hr after ischemia, and the number of the apoptotic cells increased with time and peaked at 5 hrs after ischemia, suggesting apoptosis may be a main feature of

myocardial ischemia (Hu et al., 2001). It was shown that growth factors may inhibit the development of apoptosis and hence alleviate the apoptosis of myocytes caused by ischemia-reperfusion injury. Like the growth factors, Chinese herbal drugs have gained a popular recognition in terms of myocardial preservation by apoptotic inhibition (Zhang et al., 2007).

Chinese herbal medicine was usually categorized with respect to Chinese medicinal property or the natural character. With the introduction of modern scientific technologies, novel classifications were introduced for Chinese medicine, such as drug effect, medicinal portion, botanical, zoological, mineralogical, and chemical ingredient classifications. Of them, the classification referring to the pertinent major active ingredients contained in Chinese medicine is apparently convenient for the expression of their effective mechanisms. In recent years, studies on these active ingredients of Chinese herbal drugs have become attractive, leading to an in-depth understanding of the medicinal properties. These ingredients were grouped into four classes: alkloids, flavonoids, saponins and others including coumarins and lignanoids, that are related to vascular endothelial functions (Shi and Yan, 2005). As for myocardial preservation, more components can be involved, such as carbohydrates, glycosides, amino acids, peptides, proteins and enzymes.

Chinese herbal medicine

1. Carbohydrates

1.1 Astragalus mongholicus.

Radixes of *Astragalus mongholicus* Bge and *Astragalus membranaceus* Bge are quality products of *Astragalus mongholicus*. The main components of *Astragalus mongholicus* include *Astragaloside*, *Astragalus* polysaccharides, and flavonoids, *etc.* (Huo, 2007). Total flavonoids of *Astragulus* could prevent the decrease of the NO concentration. Concomitantly, total flavonoids of *Astragulus* and *Astragaloside A* work as inotropic agents by way of increasing cAMP contents of the myocardium, and inhibiting the activity of the Na^+-K^+-ATPase on the myocardial cellular membrane, while *Astragalosides* act as free radical scavengers. *Astragaloside IV* is a leading active ingradient with inotropic effect, not only improving heart function of the experimental rats, but also avoiding an increase of the oxygen consumption of the myocardium (Fang, 2004). Total flavonoids of *Astragulus* may inhibit the increase of the intracellular calcium concentration induced by isoproterenol hydrochloride, indicating a calcium antagonism of the total flavonoids of *Astragulus* by relieving the calcium overload of the sarcoplasmic reticulum (Meng et al., 2004). An increased superoxide dismutase (SOD) and decreased malondialdehyde (MDA) and creatine phosphokinase (CPK) activities were associated with the introduction of *Astragalus mongholicus* (Li et al., 2003). Additionally, similar results for *Astragalus mongholicus* have been noted in patients with angina pectoris (Li and He, 2003). Pretreatment with *Astragalus membranaceus* significantly attenuated the daunorubicin-induced increases of reactive oxygen species, apoptosis and the secretions of lactate dehydrogenase (LDH) in cultured neonatal cardiomyocytes of Sprague Dawley rats (Luo et al., 2009). *Astragalus mongholicus* at a concentration of 100 g/L or 1000 g/L could reduce the apoptotic rate by 34.96% and 37.02%, respectively. The upgrading of the reperfusion injury salvage kinase (RISK), including PI3K-AKT and p42/44 [extracellular regulated protein kinase (ERK)1/2] could be the initiating way of *Astragalus mongholicusin* to regulate myocardial apoptosis. The mitogen-activated protein kinase signaling pathways have also been found to be under the modulation of *Astragalus mongholicus* in the *in vitro* rabbit ischemia-reperfusion injury and cultured myocyte hypoxia-reoxygenation models (Song et al. 2008).

1.2 *Lycium bararum* polysaccharides.

The botanical source of *Lycium bararum* polysaccharides is the dry mature fruit of the *Solanaceae* plant *Lycium barbarum L.* When *Lycium Bararum Polysaccharide Extract* was given via gastric lavage or intraperitoneal injection to the animals, both lysozyme and SOD activities and NO secretion were increased by resting macrophages, with the former drug route having a better effect (Zhou et al., 2000). *Lycium Bararum Polysaccharides* can promote the activities of glutathione peroxidase (GSH-Px) and SOD of the senile rats induced by D-galactose, and can further scavenge the free radicals (Chen and Chen, 2005). When free radical injuried myocytes induced by xanthine/xanthine oxidase system were treated by *Lycium Bararum Polysaccharides* (12.5 μg/mL), the myocardial ultrastructures remained almost normal (Yang et al., 2001).

1.3 *Tremella fucifamis* Berte, or, *Tremella fuciformispolysaccharide*.

Tremella fucifamis Berte is a polysaccharide with free radical scavenging and anti-lipid peroxidation effects. It is prepared and extracted from *Tremella fucifamis* by submerged cultures. *Tremella* polysaccharide can protect cardiomyocytes by suppressing the apoptosis induced by oxidative damage *in vitro*. The results suggested that *Tremella tremella* polysaccharide had dose-related anti-apoptotic and anti-oxidative effects on cardiomyocytes in D-galactose induced aging mice (Qu et al., 2009).

1.4 *Saussures involucrate*

The chemical ingredients isolated from *Saussures involucrate* has been proved to be complex, including flavonoids, alkaloids, and polysaccharides, *etc*. The half-scavenging concentration of polysaccharide of *Saussurea* was 22.0 µg/mL, with which the oxygen consumption of the mice could be reduced, and the swimming time of the animal increased. Both *hispidulin* and *acacetin* that were isolated from *Saussures involucrate* were capable of scavenging free radicals with anti-lipid peroxidation effect. The total alkaloids of *Saussures involucrate* were able to decrease the permeability of the cutaneous vessels of the rabbit, leading to a vascular contraction of the rabbit ear, which may be blocked by α-antagonist regilin. Moreover, the total alkaloids of *Saussures involucrate* could cause slowdown of the heart rate or even heart arrest of the *in vitro* rabbit heart (Yuan et al., 2004).

1.5 Polysaccharide *Krestin*

Coriolus versicolor polysaccharide is an abstract of the dry carpophore of *Polyporus Varlus* (PERS) Fr. Luo et al. (2002) administered the canine model of ischemia-reperfusion injury with oral *Polysaccharide Krestin* 150 mg/kg daily two days prior to operation. They found that these animals had better left ventricular ejection fraction and lower plasma MDA contents during early reperfusion (5- 120 mins).

2. Glycosides

2.1. Phenolic glycoside

Paeonol. Paeonol is a main active ingredient of *Cynanchum paniculatum* (Bge.) Kitag. Paeonol can decrease the cholesterol/phospholipid ratio of the mitochondrial membrane, and improve membranous Ca^{2+}-ATPase activity, membrane lipid fluidity and myocardial free fatty acid of the myocardial ischemia-reperfusion injury model in mice (Zhang and Zhang, 1994). Tang and Shi (1990) observed the Ca^{2+} influx in neonatal mice myocytes, a remarkable decrease in beating rate of the myocytes, and an inhibition of the Ca^{2+} uptake in both fast and slow phases with 50-400 µg/mL paeonol. At a dose of 400 µg/mL, it showed a similar effect on the calcium uptake in cultured myocardial cells to verapamil at 10 µmol/L.

2.2. *Anthraglycosides* and *Quinones*

2.2.1 Danshensu Salvianic acid A and Tanshinone

Danshensu Salvianic acid A showed its protective effect on myocardial mitochondria of the ischemia-reperfusion injury mice by scavenging O^- and OH^-. Working as a free radical scavenger to eradicate O^{-2}, OH^- and H_2O_2, sodium tanshinone IIA sulfonate (5 mg/kg) was able to decrease the products of MDA in the myocardium and lessened the delivery of CPK. It illustrated that as a free radical scavenger tanshinone was even superior to verapamil in terms of myocardial protection in the *in vitro* mouse heart model. Experimental studies disclosed that intravenous injection of sodium tanshinone IIA sulfonate in the canine myocardial ischemia-reperfusion injury model may lead to decreased myocardial oxygen consumption by lowering left ventricular wall stress, and brought about a decreased myocardial infarcted area with an effect comparable to dipyridamole. Tanshinone IIA may protect cultured PC12 cells from all injury models including hypoxia, hypoglucose, oxidant injury, calcium overload, NO neurotoxicity, and glutamic acid injury, especially was good for the ischemic and calcium overload injuries (He et al., 2001). In the myocardial infarction rats, sodium tanshinone IIA sulfonate significantly reduced the infarct sizes, the blood LDH level, and the number of apoptotic cardiomyocytes in the infarcted hearts (Yang et al., 2008a). Protective mechanisms of tanshinone were evidenced to be mediated by increased scavenging of oxygen free radicals, prevention of lipid peroxidation and upregulation of the Bcl-2/Bax

ratio (Fu et al., 2007a). Tanshinone IIA may inhibit the increasing sizes of the myocytes, the synthetic rate of the myocardial protein, and the apoptotic rate induced by angiotensin II, thereby decreasing the expression of the apoptotic gene Fas mRNA (Feng and Zheng, 2006). Tanshinone IIA (2 mmol/L) markedly attenuated adriamycin-induced reactive oxygen species production, and prevented the adriamycin-mediated reduction of the Bcl-2/Bax ratio as evidenced by the Western blot assay (Gao et al., 2008).

2.2.2 *Polygonum multiflorum*

Polygonum multiflorum is the dry radix of *Polygonum multiflorum Thunb*. *Polygonum multiflorum* can improve SOD activity of the myocytes, scavenge free radicals and inhibit lipid peroxidation. *Polygonum multiflorum* may significantly improve the stability of the lysosomal membrane, protect the membranal structure of the myocardium, and stabilize the cellular membrane (Jin and Jin, 2006). Experiemntal studies revealed that *Polygonum multiflorum* inhibited 52.1 ± 7.3% of the oxygen consumption and 50.9 ± 5.3% of MDA production (Hong et al., 1994). Its ability to enhance myocardial anti-oxidant status under the conditions of ischemia reperfusion-induced oxidative stress has been proved (Yim et al, 2000). *Tetrahydroxystilbene-glucoside*, one of the effective ingredients of *Polygonum multiflorum*, was tested in terms of its protective effect on rat myocardial ultrastructure. *Tetrahydroxystilbene*-glucoside even in a low dose could remarkably decrease the expression of transforming growth factor-β_1 of myocardial cytoplasm, indicating a possible inhibition on the transforming growth factor. Lower MDA levels and inducible nitric oxide synthase (iNOS) activities of the myocytes were seen in the rats administered with *tetrahydroxystilbene*-glucoside (Tang, 2006).

2.3. Flavonoids and Flavonoid glycosides

2.3.1 *Ginkgo biloba* extract (Egb761)

Egb761 is composed of flavonoids, terpenoids, phenolic compound, and amino acids, *etc*. Liebgott et al. (2000) reported two main components of Egb761, flavonoid glycosides and terpenoid, may coordinate scavenging free radicals and prevent peroxidation injury. Tosaki et al. (1994) found *EGb761* at a dose of 50 mg/kg or 100 mg/kg may significantly improve coronary flow, aortic flow, left ventricular developed pressure, and the first derivative of left ventricular developed pressure (dp/dt max). EGb761 can increase SOD activity of the cytosol, prevent mitochondrial lipid peroxidation, maintain the Ca^{2+}-ATPase activity of the mitochondrial membrane, and improve Ca^{2+} transport of the ischemic myocardium (Li et al., 2007a). Shen and Zhou (1995) found that treatment (10 mg/kg, injected into the coronary artery) resulted in significant inhibition of the lipid peroxidation and preservation of total and CuZn-SOD levels in both plasma and the myocardium during and at the end of reperfusion. Both tissue type plasminogen activator (t-PA) decrease and plasminogen activator inhibitor-1 (PAI-1) increase mediated by ischemia-reperfusion were significantly suppressed by EGb761. Egb761 can apparently alleviate the accumulation of Na^+ and Ca^{2+} and the loss of K^+ and Mg^{2+} in the ischemia-reperfusion myocardium (Deng et al., 2006). EGb761 could inhibit influx of excellular calcium of myocardium of neonatal rats (Zhang et al., 2000). Egb761 along with its monomer *Quercetin* dihydrate may inhibit myocyte hypertrophy, total protein and diameter increment, induced by angiotensin II, which could thereby promote SOD activity and decrease MDA content (Wu and Gu, 2006). Egb761 has shown an antagonistic action on platelet-activating factor, a key point of myocardial injury (Zhang and Gao, 2008). Expressions of p-ERK1/2, p-JNK and p-P38 mediated by angiotensin II increased significantly and Quercetin could apparently inhibit these expressions probably by the ROS/JNK signaling pathway. In the Egb761-treated rats, apoptosis of the cardiomyocytes decreased significantly, suggesting the protective effects of Egb761 on rat cardiomyocytes against apoptosis (Yu et al., 2007). EGb761 could typically inhibit NO release, decrease the expression of iNOS

mRNA (Varga et al. 1999), and promote Bcl-2 and Bcl-xL gene expressions of rabbit myocytes (Zhang et al., 2005a).

2.3.2 Bamboo Leaves

The active ingredients of the bamboo leaves include abundant flavanoids, polysaccharides, and trace elements, etc., with antiseptic and anti-oxidant properties (He and Yue, 2008). The Bamboo Leave Extract may increase coronary flow of the *in vitro* guinea pig heart, counteract T wave changes induced by pituitrin, and decrease the area of the myocardial infarcted area (Fu et al., 2006). Experiments proved that the bamboo leave flavonoid was comparable to Egb761 in terms of the content of the flavonoid as well as the capacity of anti-free radicals (Zhang et al. 2002a). The bamboo leave flavonoid may reduce the occurrence of myocardial apoptosis, and inhibit the expression of Bax, Cyt-c and caspase-3, but not of Bcl-2 (Fu et al., 2007b).

2.3.3 Baicalin

Baicalin is a flavonoid compound extracted from *Scutellaria baicalensis* Georgi. Baicalin significantly improved the SOD activity of the hypoxic myocytes of neonatal Sprague-Dawley rats at a concentration of 0.1-10 μg/mL, inhibited MDA production at a concentration of 1 μg/mL, and inhibited NO secretion at a concentration of 10 μg/mL (Liu et al., 2003a). When baicalin 10-40 mg/kg was given to the rats 5 mins before ligation of the coronary artery, the post-**infarction heart function** improved with decreased MDA content and increased SOD activity (Liu et al., 2003a). Woo et al. (2005) proposed that the cardioprotective effect of baicalin may not be due to its anti-oxidant effect, because they observed an adverse rather than a protective effect when baicalin was present during hypoxia. Pretreatment of neonatal rat cardiomyocytes with baicalin up to 10 μmol reduced LDH delivery significantly, while pretreatment with baicalin up to 100 μmol was ineffective. In the rat model, baicalin may improve CPK and LDH contents as well as myocardial ultrastructure (Ouyang et al., 2006). The protective effects of baicalin on heart injury of rats with severe acute pancreatitis led to better results in the rat mortality, pathological changes of heart, NF-κB, P-selectin, Bax, Bcl-2, and caspase-3 protein expression levels (Xiping et al., 2007).

2.3.4 Carthamin yellow

More than 60 chemical components have been isolated from the safflower including flavonoids, lignins, and acetylenics, *etc*. Carthamin yellow (also named saffloryellow) and hydroxysaffloryellow A are the main effective components. Carthamin yellow significantly reduced the LDH and MDA levels, and alleviated free radical damage (Zhang et al., 2003a). Effective ingredients of Safflower can influence immune system, block platelet-activating factor receptors, increase NO level and eradicate free radicals. Saffloryellow can inhibit Na^+-K^+-ATPase activity and increase cAMP content of the myocardium during ischemia-reperfusion (Cheng et al., 2000). Piao et al. (2002) found that in the coronary perfusion experiments in rats intraperitoneal injection of Carthamin yellow 0.8-1.25 g/kg could remarkably improve the ischemic electrocardiographic changes induced by isoproterenol, reflecting an antagonistic action on the adrenergic receptors. Mo et al. (1995) found that Carthamin yellow Extract (5-500 mg/mL) blocked calcium influx induced by noradrenaline and hyperkalemic solution, showing a dose-effect relationship similar to but weaker than that of verapamil. Safflower injection preserved rat heart displayed improved ultrastructures compared with the control, with higher SOD activity and lower MDA content (Zhang and Shi, 2003). *Carthamus tinctorius* extract was associated with a decreased apoptotic index, decreased expression of

Bax, and upregulation of Bcl-2 (Chen and Zheng, 2006).

2.3.5 *Erigeron breviscapus* (Vant.) Hand-Mazz

It is the whole plant of *Compositae erigeron breviscapus* (Vant.) Hand. Mazz. Components extracted and differentiated from the *Erigeron breviscapus* (Vant.) Hand-Mazz include flavonoids, caffeate, and phenolic acids, etc. Of them, flavonoids had strong non-competitive inhibiting effect on protein kinase C, thereby alleviating ischemic injury (Zhou et al., 2002a). The effective ingredient *Erigeron* is an inhibitor of protein kinase C, which participates in ischemic neuron injury, and plays an important role in the cellular signaling pathways of neuron apoptosis (Lei et al., 2002). *Erigeron* could promote myocardial SOD, and decrease myeloperoxidase activities, by which accumulation of free radicals in the myocardium could be decreased and myocardial injury induced by isoproterenol was alleviated. Blockage of the calcium channel of the myocytes with a decrease of calcium influx was observed when *Erigeron* was used. *Erigeron* also displayed its effects in promoting SOD, nitric oxide synthase (NOS) and NO levels in the hypoxic rat model (Mao et al., 2004). Zhou et al. (2002b) noted *Erigeron* was useful in regressing left ventricular remodeling by improving cardiomyocyte hypertrophy, and decreasing collagen volume fraction in spontaneous hypertensive rats. *Erigeron* could significantly decrease the number and percentage of apoptotic nuclei of the myocardium, and upregulate the expression of apoptosis-inhibiting gene Bcl-2 mRNA (Liu and Chen, 2004). In male Sprague-Dawley rats, the myocardial infarct size was significantly reduced by scutellarin (15 and 50 mg/kg), an active molecule existing in *Erigeron breviscapus* (Vant.) Hand. Mazz, but not by breviscapine (5 to 50 mg/kg); and the anti-myocardial infarction effect of scutellarin was dose-dependent. Compared with the control group, scutellarin (50 mg/kg) remarkably reduced the myocardium cell apoptosis in myocardial myocardial infarction rats (Lin et al., 2007).

2.3.6 Puerarin

Puerarin is an isoflavone extracted and isolated from the dry roots of the legume *Pueraria Lobata* (Willd) Ohwi. Puerarin could significantly decrease the CPK delivery of the myocardium. The heat shock protein 70 expression was much higher in rats receiving *Puerarin* compared to those subjected to ischemia-reperfusion (Tang et al., 2007). A significant decrease in MDA, NO and NOS levels and the leakage of LDH, and a rise in SOD activity occurred in the Puerarin Group (Yan et al., 2005). Puerarin may also regulate plasma endothelin and NO contents, hence improving the NO/endothelin ratio (Wang and He, 2004). In the rat hearts pretreated with 0.24 mmol/L Puerarin for 5 mins, a significant inhibition of Ca^{2+}-induced mitochondrial swelling was observed (Yang et al. 2008b). In the mitochondria isolated from the rat hearts pretreated with 0.24 mmol/L Puerarin for 5 mins, a significant inhibition of Ca^{2+}-induced swelling was observed, and this inhibition was attenuated by 5-hydroxydecanoate (Gao et al., 2005). *Puerarin* showed a decrease in apoptosis of the ischemia-reperfusion myocardium in rats, where the apoptotic cells were significantly reduced during the reperfusion period. Experimental studies showed that it inhibited cellular apoptosis during myocardial ischemia-reperfusion injury, increased the expression of Bcl-2, and decreased the expression of Bax (Yan et al., 2005). Puerarin (120 mg/kg/day, intraperitoneal injection) could increase serum nitrite concentration in rats with myocardial ischemia, and induce transcriptional or protein level expressions or activation of endothelial NOS, and the Akt/protein kinase B phosphorylation (Zhang et al., 2008a).

2.3.7 Total flavonoids of hawthorn leaves

Total flavonoids of hawthorn leaves could alleviate arrhythmias, delay the

arrest time, and decrease LDH delivery and MDA contents, and increase intracellular SOD activity and NO content of the myocytes of the ischemia-hypoxia model in 3-day Sprague-Dawley neonatal rats (Ye et al., 2005). Flavonoids of hawthorn leaves (12.5, 25.0, and 50.0 mg/kg) could alleviate ST segment changes of the rat heart due to ischemia-reperfusion injury (Min et al., 2007).

2.3.8 *Portulaca oleracea* L.

Portulaca oleracea L. is the whole plant of purslane of the family *Portulacaceae*. *Portulaca oleracea L.* contains n23 fatty acids, anti-oxidants, amino acids, and trace elements, which are effective cardiovascular components. Total flavonoids of *Portulaca oleracea L.* showed inhibiting actions on pyrogallol autoxidation in a direct dose-effect relationship (Lu et al., 2004).

2.4. Saponins

2.4.1 *Raidix ophiopogonis*

Raidix ophiopogonis is a liliaceous plants, and the product currently available commercially in our country is the radix of *Ophiopogon japonicus* (Thunb.) Ker-Gawl. Acting as nourishing yin, and promoting fluid production, it has been found to have multiple pharmaceutical effects including two-way regulations of blood glucose and immunologic function, antibiosis, anti-cancer, and in particular cardiovascular effects. *Ophiopogon* polysaccharide and *Ophiopogonin* (60 g raw material/kg, via gastric lavage) could increase myocardial nutrient flow in a dose-effect relationship (Zhou et al., 2003). *Ophiopogcnin* may act on the Na^+- and Ca^{2+}-channels to decrease the influx of these ions, and it was effective to remarkably increase the reduced expression of Bcl-2 gene, and alleviate calcium overload in the subject and thereby treat the peroxide-induced condition (Zhang et al., 2003b).

2.4.2 Ginsenosides

Radix Ginseng is from *Panax Ginseng*, a herbaceous plant of the *Araliaceae* . The chemical components include ginsenosides, *ginseng* polysaccharides, and active peptides, etc. Ginsenosides can limit myocardial infarction size, regulate metabolism of arachidonic acid, and increase the 6-Keto-$PGF_{1\alpha}$/TXB_2 ratio (Li et al., 2006). The optimal concentration of ginsenosides for myocardial protection was 20-80 mg/L, however, this drug may show a harmful effect on the myocardium when the concentration was 160 mg/L (Chen et al., 1994). Yuan et al. (1997) obtained a similar result in a cardiac concordant xenotransplantation rat model where the proper concentration of the drug was 40 mg/L; whereas the protective effect diminished and it may jeopardize the myocardium when the concentration was 320 mg/L. They demonstrated that the Rb component may predominate at a lower concentration, while the harmful component may function instead at a higher concentration. Zhang et al. (1998) found that ginsenosides Rb1, Rb2 and Rb3 worked as both anti-oxidant and calcium channel blockage by protecting myocytes from apoptosis during ischemia-reperfusion. Both Rb1 and Re significantly stimulated the NOS activity in a concentration-dependent manner. It demonstrated a direct depressant action of ginsenosides on cardiomyocyte contraction, which may be mediated in part through the increased NO production (Scott et al., 2001). The typical apoptotic features in the rat myocardium with ischemia-reperfusion injury could be improved with the use of ginsenosides while the intracellular expression of Bcl-2 gene was significantly increased (Zhou and Xu, 2001). In the rat ischemia-reperfusion injury model, ginsenoside Rb, lavage for consecutive 7 days may reduce serum enzymatic activities and MDA content, while increasing, SOD and GSH-Px activities, and justifying the PGI_2/TXA_2 ratio (Qu et al., 2007).

2.4.3 *Panax quinquefolium* L.

Panax quinquefolium L. is a perennial persistent root herb of the *Araliaceae*. Its bioactive materials are saponins, polysaccharides, flavonoids, essential oils and trace elements, etc. *Panax quinquefolium* total saponins (30, 100, and 300 µg/mL) could decrease the delivery of aspartate aminotransferase, CPK and LDH in the isolated rat heart Langendorff model (Cao et al., 2003). Intraduodenal administration of ginsenosides from the leaves and stems of *Panax quinquefolium* to the myocardial ischemic models of dog and rabbit led to a reduced infarction area, reduced serum levels of free fatty acid and MDA, decreased LDH, CPK and aspartate aminotransferase, and an increased SOD activity (Ding et al., 2002). At a concentration of 1.5 mg/mL, it may inhibit the increase of the intracellular calcium comparable to the effect of verapamil (0.5 µmol/L) (Guan et al., 2004). *Panax quinquefolium* total saponins could decrease the left ventricular load, and decrease myocardial oxygen consumption, and increase the blood supply to the ischemic myocardium (Liu et al., 2001). *Panax quinquefolium* buffered significantly the changes in the ventricular weight and cardiac coefficient of the ventricular remodeling rats, and improved the arterial pressure, and the left ventricular end diastolic pressures. *Panax quinquefolium* also inhibited the thickening of the cardiac muscle fibers and improved myocardial interstitial edema, showing same effects as angiotensin converting enzyme inhibitor benazepril (Ju et al. 2007). *Panax quinquefolium* could significantly improve the endothelial function and prevent from ventricular remodeling post-myocardial infarction, regulate the lipid metabolism and increase the PGI_2/TXA_2 ratio (Fan et al., 2009). Improved expressions of vascular endothelial growth factor and basic fibroblast growth factor in the infarcted myocytes, with increasing vasogenesis in the ischemic region have been shown in the *panax quinquefolius* saponin-treated rats (Wang et al., 2007a). The use of *panax quinquefolium* correlated with a significant reduction in apoptosis in rats after acute myocardial infarction, and a downregulation of Fas and an upregulation of Bcl-2 protein expressions in rats (Yin et al., 2005).

2.4.4 *Notoginseng* Saponins.

Notoginseng is the radix of *Ranax Notoginseng* (Burk) F. H. Chen, a perennial herbaceous plant. The main active component of *Notoginseng* is *Panax Notoginseng* saponins. Li et al. (1990) found that *Panax notoginseng* saponins reduced the infarcted area, and decreased CPK release of the myocardium of rats with coronary artery ligation and recannalization. *Panax Notoginseng* saponins could improve the Ca^{2+} pump activity on the membranes of myocardial sarcoplasmic reticulum, reduce myocardial intracellular Ca^{2+}, and inhibit left ventricular remodeling (Deng, 2007). Pretreatment with *Panax Notoginseng* saponins significantly protected the mice from doxorubicin-induced cardiotoxicity as evidenced from improved ventricular contractile function, lower levels of serum LDH, CPK and CK-MB, minimal morphological changes in the hearts, and normalization of myocardial SOD, GSH-Px and catalase activities (Liu et al., 2008). *Notoginseng* saponins significantly improved myocardial NO level and constitutive NOS activity , lowered collagen content and iNOS activity, and inhibited cardiac hypertrophy in the myocardial hypertrophy rat model induced by isoproterenol (Zhou et al., 2006). Inhibited tumor necrosis factor (TNF)-α delivery, NF-κB activation and neutrophil infiltration and decreased ICAM-1 expression were seen with *Notoginseng* saponins pretreatment (Gu et al., 2005; Tang et al., 2003). *Notoginseng* saponins had an apparent inhibitory effect on cellular apoptosis induced by angiotensin II. *Notoginseng* saponins (50 mg/L) showed a remarkably decreased myocardial apoptotic rate and a more alleviated calcium overload comparing to Angiotensin II Group (Chen et al., 2005). The *Notoginseng* saponins-administered endothelial cells showed a much lower apoptotic rate, with downregulation of Fas expression and upregulation of Bcl-2 (Lǚ and Liang, 2005).

2.4.5 Gross saponins from *Tribulus terrestris*

Gross saponins from *Tribulus terrestris* could decrease the apoptotic rate at any dose, but a large dose may upregulate, while a small dose may downregulate Bcl-2 expression. Besides, it may significantly decrease the TNF-α and interleukin (IL)-1β contents with obvious NF-κB p65 nucleus translocation at any dose in an Sprague-Dawley neonatal rat model of myocardial ischemia-reperfusion injury (Yin et al., 2006). It may also promote δPKC and εPKC expressions in neonatal rat model of hypoxia (Sun et al., 2008).

2.4.6 Sasanquasaponin (SQS)

Sasanquasaponin is a mixed saponin extracted from the dregs after oil extract of the seeds of the *Theaceae* plant *Camellia oleifera Abel*. Sasanquasaponin has shown its anti-Na^+-Ca^{2+} overload effect by decreasing Mg^{2+}, and increasing Na^+ and Ca^{2+} contents, and decreasing the Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase activities of the mitochondria of rat myocardial ischemia model (Li et al., 2007b). It reduced LDH release and increased the cell viability in a dose-dependent manner up to 10 μmol and concomitantly decreased MDA and oxidized glutathione contents, while significantly increased the activities of SOD (Chen et al., 2007). By using an NO delivery antagonist, the pretreating effect of *Sasanquasaponin* was weakened or abolished, suggesting that this agent may work at least partly by activating NOS and inducing the formation of NO and adenosine (Huang et al., 2001).

2.4.7 Gypenosides

Gypenosides are saponins derived from *Herba Gynostemmatis,* the dry whole plant of *Gynostemma pentaphyllum* (Thunb.) Mak. of *Cucurbitaceae* family. Experiments revealed that Gypenosides may reduce myocardial MDA content, and inhibit the delivery of serum CPK and plasma endothelin in the rat model of myocardial ischemia-reperfusion injury, and remarkably increase myocardial SOD and plasma NO levels, balancing the NO/endothelin ratio (Zheng et al., 2002). The cardioprotective effect of Gypenosides may also depend on calcium overload amelioration and abnormal excitement inhibition (Qi and Zhang, 2003). Moreover, Gypenosides inhibited *c-fos* gene expression in a dose-dependent manner with decreasing concentrations, while it showed no influence on *sis* gene expression (Qi and Zhang, 2003). Tanner et al. (1999) found that the extract of *Gynostemma pentaphyllum* at 0.1-100 μg/mL elicited concentration-dependent vasorelaxation of porcine coronary rings that was antagonized by the NOS inhibitor N(G)-nitro-l-arginine methyl ester. Indomethacin had no significant effect on *Gynostemma pentaphyllum*-induced relaxation. The results demonstrated that the extracts of *Gynostemma pentaphyllum* directly stimulated NO release, but not the prostanoid production. The expression of TNF-α was significantly increased in the Ischemia-Reperfusion Group (Zheng and Zheng, 2007). Compared with the Hypoxia-Reoxygenation Groups, the positive expression index of Fas/FasL proteins were significantly lower in groups with different doses of total flavones of *Gynostemma pentaphyllum* (Thunb) Mak., suggesting that the total flavonoids could protect the myocardium against hypoxia-reoxygenation injury by decreasing the production of TNF-α, downregulating the protein expression of Fas/FasL genes, and inhibiting myocyte apoptosis (Li et al., 2007c).

2.4.8 Dioscin

Dioscin exists extensively in *Dioscoreaceae*, *Liliaceae*, and the legume plants. It can be used for the purposes of eliminating phlegm, desensitization,

anti-inflammation, anti-tumor, protection against myocardial ischemia, decreasing blood viscosity, reducing platelet aggregation, and decreasing triacylglycerol, *etc.* (Zhao et al., 2008). Dioscin could alleviate calcium overload of the experimentally hypoxic myocytes (Liu et al., 2004a). In the rat models of myocardial ischemia-reperfusion injury, either a high dose dioscin (300 mL/kg/day) or a low dose dioscin (150 mL/kg/day) may lead to a smaller myocardial infarction size and better cardiac function comparing to the control (Zhao et al., 2008). The *in vitro* Sprague-Dawley neonatal rat model of myocyte hypoxia showed decreased LDH (4.534 ± 0.872 U/L), cardiac Troponin I (0.682 ± 0.091 µg/mL) levels and a decreased intracellular free calcium concentration (479.99 ± 57.94 nmol/L) when treated with dioscin. Experiments also revealed that dioscin alleviated the calcium overload of the hypoxic myocytes by enhancing the expression of calcium pump *SERCA2* on the sarcoplasmic reticulum (Liu et al., 2004b). High dose of dioscin (100 mL/L) resulted in a higher SOD activity, and lower MDA and NO contents comparing to the normal control and the hypoxia/reoxygenation groups (Ni et al., 2007).

2.4.9 Total saponins of *Semen Ziziphi spinosae*

Total saponins of *Semen Ziziphi spinosae* are a kind of effective components extracted from Chinese medicine obtained from the seed of *Ziziphus spinosa* Hu. These agents had shown blood pressure lowering, anti-arrhythmic and anti-ischemic effects. In the anoxia-reoxygenation model of cultured neonatal rat myocytes, total saponins of *Semen Ziziphi spinosae* could markedly and dose-dependently decrease MDA content, elevate SOD activity and increase membrane fluidity, proving an effect of anti-peroxidation induced by anoxia-reoxygenation (Wan et al., 1995). In cultured neonatal rat myocytes, the increase of LDH release from the damaged myocardial cells induced by oxygen-glucose deprivation, ehlorpromazine or mitomycin C could be attenuated by *Ziziphi spinosae* (33 µg/mL) (Chen et al., 1990). Compared with the control, the experimental group treated with *Semen Ziziphi spinosae* showed significantly smaller myocardial infarcted area, and significantly decreased ST segment and T wave on electrocardiogram (Zhang et al., 2005b).

2.4.10 Paeoniflorin

Paeoniflorin is extractable from the radix of *Paeonia albifolra* Pall. Paeoniflorin can inhibit platelet aggregation, dilate coronary arteries, increase coronary flow, and protect acute myocardial ischemia. However, the exact cardiovascular mechanisms of Paeoniflorin remain unclear. Paeoniflorin showed an interdiction to L-type calcium channels in the isolated rat myocytes for patch clamp research, but lack of frequency-dependent inhibition (Zhang et al., 2003c). High-dose of Paeoniflorin remarkably decreased the hazard index, lowered myocardial CPK and LDH, and reduced the apoptotic index (Zhang et al., 2008b. Both paeoniflorin and paeonol, two main active compounds of the *Paeonia albiflora Pallas*, were shown to lead to a reduced myocardial infarct size in rats through protection from apoptosis (Nizamutdinova et al., 2008).

2.4.11 Hyperin

Hyperin is a common component of many Chinese herbal drugs. Hyperin (12.5, 25 mg/kg/day × 3, intraperitoneal injection) decreased rat myocardial infarcted area, inhibited serum CPK and LDH elevation, and promoted myocardial SOD content (Li et al., 2001a). Hyperin (25, 50 mg/kg) had obvious protective effect on rat myocardial apoptosis 3.5 hrs after reperfusion, and Hyperin (0.5-50.0 µmol/L) may reduce the apoptosis formation in rat myocyte with hypoxia-reoxygenation (Li et al., 2002a), and inhibit dose-dependently LDH delivery and calcium overload in the myocytes (Li et al., 2001a). Hyperin at 12.5 µg/mL, 50 or 12.5 µg/mL, and 50 µg/mL,

50 or 12.5 µg/mL was found to have a protective effect on myocardial injury caused by adriamycin, by mitomycin, by oxygen-glucose deprivation or by hypoxia-reoxygenation (Xu et al., 2000).

2.4.12 *Acanthopanax Senticosus* Saponins or *Acanthopanax senticosides*

Radix Acanthopanacis Senticosi is an *Araliaceae* plant, with a botanical name of *Eleutherococcus senticosus* (Ruper.et Maxim.) Maxim., containing *eleutherosides* A~G, I, K, L, and M. *Acanthopanacis Senticosi* could improve T wave elevation and decrease of heart rate in the rabbit myocardial ischemia model subjected to pituitrin injection, and promote regeneration of the surface cells. In such a model, rat myocardial ischemia was significantly improved with a preserved SOD activity and a reduced MDA production. *Acanthopanacis Senticosi* could markedly increase calmodulin content, suggesting that a nucleic acid system pathway might be followed by *Acanthopanacis Senticosi* in improving heart function (Wang and Juan, 2005). Treatment with *Acanthopanax senticosus* significantly improved the survival rate of mice. *Acanthopanax senticosus* pretreatment inhibited the elevation of TNF-α, and decreased the iNOS level in serum and liver, and inhibited the NO overproduction (Lin et al., 2008). Total saponins from the leaves of *Acanthopanax Senticosus* could weaken the contractility of isolated Wistar rat heart in a significant dose-dependent manner, in accordance with what was noted in a weakened excitation-contraction coupling. *Acanthopanax senticosides Sb* (50-200 mg/L) was found to decrease action potential of cultured Wistar rat myocytes, which could be reversed by Ca^{2+} 80 mg/L, showing a similar calcium channel blocking effect to nimodipine (Zhan et al., 1995).

2.5. Coumarin

2.5.1 *Andrographis paniculata*

Andrographis paniculata is the dry aerial part of the *Acanthaceae* plant *Andrographis paniculata* (Buri. f.) Nees. Present studies on *Andrographis paniculata* concentrate on *Andrographolide* and the flavonoid component API0134. This flavonoid component API0134 could improve canine heart function, decrease the extent of myocardial infarcted area, alleviate the extent of myocardial injury, and decrease the occurrence of arrhythmias. Meanwhile, it could promote the production of prostaglandin, raise the PGI_2/TXA_2 ratio, and inhibit the granulocyte from producing free radicals. API0134 had an extensive scavenging function on H_2O_2, O^{2-}, and ·OH, and inhibited the induced aggregation of human-washed platelets. Prophylactic API0134 for 4 and 8 weeks significantly raised NO and cGMP contents and SOD activity, and decreased endothelin and lipid hydroperoxide contents (Zhang et al., 2002b), and maintain the NO/endothelin balance (Wang et al., 2003). API0134 (50 mg/kg, i.v.) in rabbits may raise the cAMP level, slightly increase cGMP, alleviate degranulation and decrease cytoplasmic calcium concentration (Wu et al., 2002). Alleviation of calcium overload by API0134 may also be contributable to the effect of promoting Na^+-K^+-ATPase and Ca^{2+}-ATPase activities on the cellular membrane of the myocardium. The cardioprotective effect of *andrographolide* was in a time-dependent manner with upregulation of glutathione (Woo et al., 2008). *Andrographolide* may dose-dependently upregulate ICAM-1 expression induced by TNF-α, and inhibit apoptosis. *Andrographolide* could inhibit cytochrome C from entering into the cytoplasm and eliminate mitochondrial potential energy, thereby preventing from activations of caspase-3 and -9, and inhibiting the mitochondrial pathway of apoptosis. *Andrographolide* may induce the activation of an anti-apoptotic signaling protein kinase Akt and phosphorylation of the pro-apoptotic molecule BAD (Liu et al., 2003b).

2.5.2 Praeruptorin C

Praeruptorin C is an effective component extracted from *Peucedanum praeruptorum* Dunn., with effects of vascular dilation, myocardial contractile inhibition, and myocardial compliance improvement. Praeruptorin C can inhibit myocardial LDH delivery, increase intracellular SOD concentration in the neonatal rat model of myocyte damage (Zheng et al., 2007). Intraperitoneal injection of praeruptorin C can alleviate myocardial ischemia-reperfusion injury, promote coronary flow recovery, prevent the decrease of left ventricular systolic pressure and the dp/dt max, and inhibit CPK delivery, with similar effects to nifedipine (Yang et al., 1992). The Na^{+}-Ca^{2+} exchanger mRNA level was much lower in neonatal rat myocytes with praeruptorin C pretreatment than that of the Ischemia-Reperfusion Group (Xi et al., 2008). Praeruptorin C showed predominant pharmacological actions of lowering blood pressure and dilating the coronary arteries with a possible mechanism of calcium antagonism (Kong et al., 2002). Comparing with the Hypoxia-Reoxygenation Group, the LDH value, intracellular calcium fluorescence intensity level, and cellular apoptotic index were remarkably decreased (Chen and Zhu, 2007).

3. Lignanoids

3.1 Fructus schisandrae chinensis

The effective components of *Fructus schisandrae chinensis* are lignanoids, essential oils, organic acids, and polysaccharides, etc., with lignanoids being the most important one, contained 19.2% in the fruits. *Schisandra chinensis* Baill Extractum had a strong protective effect on hypoxic or ischemic injury in animals. It significantly extended the survival time of the animals in the condition of constant pressure and hypoxia, and significantly improved the T wave changes on electrocardiogram induced by pituitrin (Lin et al., 1998). The protective effects of this agent were experimentally observed as to increase SOD activity of erythrocyte, markedly lowered the lipid hydroperoxide content of the venous blood, and lessen the myocardial infarct extent (Guo et al., 2006).

4. Essential oils

4.1 *Radix angelica sinensis*

Radix angelica sinensis is the dry root of *Angelica Sinensis* (Oliv.) Diels, a spignel plant. *Radix angelica sinensis* has antagonistic effects on oxidized low density lipoprotein thereby leading to a reduced NO secretion of the endothelial cells and an increased ICAM-1 expression. The possible mechanism may be associated with the cholinergic receptor. *Radix Angelica sinensis* injection was proved to have a myocardial protective effect by way of calcium influx blockage similar to that of verapamil. *Radix Angelica sinensis* extract may improve anti-oxidant capacity, activate ERK signaling transduction pathway, and enhance the expression of endothelial NOS. *Radix angelica sinensis* could upregulate the expression of Bcl-2 and downregulate the expression of Bax, causing a decreased Bax/Bcl-2 ratio, so that apoptosis of the myocytes could be inhibited, and left ventricular function and ventricular remodeling improved (Shangguan et al., 2008). *Radix angelica sinensis* injection could effectively inhibit myocardial hypertrophy induced by angiotensin II (Yu et al., 2006). In the *Radix angelica sinensis* injection treated rats, the expression of P57kip2 protein was strong (Feng et al., 2008b), whereas the expression of cyclin-dependent kinase-2 protein in the myocytes was weak, suggesting that *Radix angelica sinensis* may have an impact of positive cell-cycle regulating agent (Feng et al., 2008a).

4.2 *Rhizoma Chuanxiong*

Rhizoma Chuanxiong is the dry rhizome of *Ligusticum Chuanxiong* Hort, a spignel plant. Chuanxiong-pathalide A can increase coronary flow and myocardial contractility, and can significantly improve the delivery of LDH, MDA and SOD in an isolated rat heart model of ischemia-reperfusion injury. Increased NO and NOS activities were observed in culture solution of the Chuanxiong-pathalide A Group, associated with a reduced endothelin activity, an increased iNOS mRNA, and a decreased endothelin mRNA expression (Gao et al., 2007). Ligustrazine, with a chemical name of tetramethylpyrazie (TMP), is the key component of Chinese herb *Rhizoma Chuanxiong*. Ligustrazine obviously alleviated the degeneration and necrosis, and reduced the infiltration of inflammatory cells of the ischemic myocardium of rat ischemia-reperfusion model (Li et al., 2004). The mechanisms were surmised to be the inhibition of the mitochondrial calcium overload, and the decrease of the mitochondrial NOS activity. *Ligustrazine* injection, containing 25 mg/mL of the drug, promoted the syntheses of proteins and RNA of the myocardium with oxygen-glucose deprivation, and enhanced the expression of constitutive NOS mRNA (Tan et al., 2006). To strengthen the expression of NOS gene was hence regarded as the main strategy of the prevention and treatment of oxygen-glucose deprivation. Moreover, ischemia-reperfusion may induce myocyte apoptosis and upregulate c-fos gene expression of the myocardium (Li et al., 2000, hence Ligustrazine might have played a protective role by attenuating c-fos gene expression and apoptosis (Yi et al., 1995).

5. Alkaloids

5.1 *Leonurus japonicus* Houtt

Leonurus japonicus Houtt was found to have a good effect on myocardial ischemia-reperfusion injury by protecting anti-oxidation system. relieving lipid peroxidation, protecting myocardial ATPase, and alleviating calcium overload (Zhao et al., 2004). In experimental rats, *Leonurus Japonicus* injection 0.8 mg/100 g body weight was given intravenously immediately after the ligation of the left anterior descending coronary artery, resulted in an elevated SOD activity, reduced MDA, LDH and CPK contents, decreased arrhythmic rates and better morphological changes of the myocardium (Shang et al., 2007).

5.2 Tetrandrine

Tetrandrine mainly exists in the root of *Stephania tetrandra S.* Moore, a perennial woody liana. Tetrandrine has calcium antagonism and strong non-specific anti-inflammatory effects, and can effectively prevent the inflammatory reaction during myocardial ischemia-reperfusion. Deng et al. (1993) found that tetrandrine predominently inhibited the isolated rat heart from delivering LDH and proteins from the myocardium with calcium overload, reduced myocardial infarcted size and led to declined inflammatory parameters, such as IL-1, TNF-α, platelet-activating factor, and myeloperoxidase, *etc*. Guan et al. (1998) obtained similar results in canine models. They observed that the myocardial infarct size was much smaller and IL-6, TNF-α, and myeloperoxidase levels were much lower in the Tetrandrine Group than the control. At 32 μmol/L, it showed negative inotropic action on the isolated cat papillary muscle, inhibiting the contractility induced by adrenalin, and the increase of ±dp/dt max (Jiang et al., 2002). The negative inotropic action was frequency- and voltage-dependent, and could be reversed by external calcium supplement. Tetrandrine could decrease the activity of the Ca^{2+}-ATPase of the

endoplasmic reticulum, compatable to nifedipine. Tetrandrine pretreatment could reduce the production of TNF-α and inhibit the activation of NF-κB during myocardial ischemia (Wang et al., 2007b). In the Tetrandrine Group, the LDH activity and MDA content decreased and SOD activity increased (Chen et al., 1998). Tetrandrine pretreatment remarkably lessened myocardial ischemia-reperfusion injury. Comparing with sham, tetrandrine had much less apoptotic myocytes, and a much smaller apoptotic index (Chang *et al.*, 2006a). Zhang et al. (2003d) found a much lower apoptotic rate (mean 3.2%) in the Tetrandrine Group of Sprague-Dawley neonatal rat model of myocardial ischemia-reperfusion.

5.3 Berberine

Berberine is an isoquinoline alkaloid found in such plants as *Berberis*, goldenseal (*Hydrastis canadensis*), and *Coptis chinensis*. Berberine could decrease calcium influx, stabilize the cellular membrane, and prevent cell necrosis. Berberine had positive inotropic action and improved heart function of heart failure patients (Cui, 2006). In mice Langendorff heart perfusion model, berberine 0.5 mmol/L added into modified Euro-Collins led to a better left ventricular peak systolic pressure and dp/dt max results and less myocardial water content comparing to the control (Luo et al., 2000). The administration of berberin (5, 10 and 20 mg/kg, respectively) and positive control drug-Captopril (45 mg/kg) for consecutive 10 weeks had relieving effects on hydroxyproline content and interstitial collagen volume fraction in the rat model with hypertrophic cardiomyopathy induced by pressure-overload, indicating that berberin may relieve the ventricular remodeling through inhibiting the fibrosis of myocardial interstitium (Hong et al., 2006).

6. Amino acids, peptides, proteins and enzymes

6.1. *Cordyceps sinensis*

Cordyceps sinensis is abbreviated as worm grass. It is a complex incorporating a stroma of fungi from *paecilomyces* and the cadaver of its host *Hepialidae Hepialus armoricanus*. Natural *Cordyceps sinensis* contains 25% protein, 8.4% fat, 18.5% fibre, 29% carbohydrate and 4.1% aldosterone-stimulating hormone. Besides these compounds there are uridine, 2,4-Dichloropyrimidine, adenine, adenosine, mannitol, ergosterol and stearic acid, *etc*. *Cordyceps sinensis* contains a lot of polysaccharides, accounting for 3%-8% of the total dry weight. In the cultured *Cordyceps sinensis*, polysaccharides are secreted from the mycelium. Chiou et al. (2000) discovered that *Cordyceps sinensis*-induced vasorelaxation was mediated by the endothelium possibly by stimulating the release of NO and endothelium-derived hyperpolarizing factor in a dose-dependent manner. *Cordyceps sinensis extracts* could promote NOS activity, and produce biological effects like NO production and coronary artery dilation, except for that they may decrease myocardial infarct size, inhibit serum CK-MB and LDH elevation, improve SOD activity and decrease MDA content (Liu et al., 1999). Liu et al. (1999) tested 20% solution of the ethanol extracts of *Cordyceps sinensis* 100 mL at a concentration of 0.2 mL drug solution in one litre of Krebs-Henseleit-Bicarbonate solution in the Langendorff rat heart model, and found that the extracts improved myocardial metabolism and attenuated myocardial damage by decreasing myocardial MDA contents and preserving myocardial ATP, ADP and AMP. Yamaguchi et al. (2000) found that the water extracts of the fruiting bodies of cultured *Cordyceps sinensis* significantly suppressed the increased serum lipid peroxide level but not other lipid levels in a dose-dependent manner in the atherosclerotic mice. Such preparations could decrease the calcium concentration of the normal myocytes as well, and therefore alleviate calcium overload of the hypoxia-reoxygenation myocytes (Yu et al., 1998).

7. Other

7.1. **Allicin**

Allicin is a kind of anti-bacterial substance in the squamous bulb of ***Allium sativum L.*** Allicin could improve the left ventricular dp/dt max, left ventricular systolic pressure, left ventricular end diastolic pressure and endothelin values of the rabbit with acute ischemia-reperfusion injury (Liao et al., 2001). Allicin could promote SOD and GSH-Px activities, reduce plasma endothelin level, balance endothelin and NO, and thus improving vascular endothelial function (Li et al., 2001b; Li et al., 2002b). Allicin was more resistant to apoptosis of cultured hypoxia/reoxygenation myocytes of the neonatal rat (Shi et al., 2006).

Discussion

Chinese herbal medicine consists of complex chemical components, showing relationships with their bioactivities. Active ingredients were defined as ingredients of herbal medicines with therapeutic activity, where one or more chemical agents from a single or compound drugs should be over 50% (80%, if in a form of injection) of the total extracts (Sun, 2004). The main effective components include carbohydrates, glycosides, lignanoids, alkaloids, amino acids, peptides, proteins and enzymes. Clinical observations in patients with coronary heart disease and angina pectoris showed cardioprotective effects of preparations of some Chinese herbal drugs, such as ***Radix puerariae, Ginkgo biloba L., Radix salivae miltiorrhizae, Astragalus membranaceus Bge, Radix acanthopanacis semticosi, Chuanxiong rhizome, Allii sativi,*** and ***Notopterygium incisium,*** etc. (Hu and Yan, 2002). Besides, myocardial ischemia-reperfusion experiments were made in animals by coronary artery occlusion (ligation, balloon compression, or thromboembolism), drug induction (pituitrin- or ergometrine-induced coronary arterial spasm, or isopreterenol increased myocardial oxygen uptake), or ***in vitro*** (the Langendorff reperfusion model, or isolated heart, myocardial slices or cultutured myocytes subjected to ischemia) (Ni, 2004). The exact mechanisms of the therapeutic effects of Chinese medicine remain unclear (Ho and Jie, 2007). However, modern studies revealed that the possible cardioprotective mechanisms of the herbal agents were multifactorial, including improving haemodynamic haemorrheology, modulating vasoactive substance and calcium balance, protecting chondrosome, inhibiting apoptosis, clearing free radicals, and promoting vasogenesis (Zhang et al., 2007).

A polysaccharide is class of relatively complex, high-molecular weight carbohydrates consisting of long-chains of serial monosaccharides joined together by the glycosidic bonds. It exists extensively in the cellular membrane of animals and the cellular wall of the plants and microorganisms. Polysaccharides of Chinese medicine have been noted to have a lot of pharmaceutical effects such as immune modulations, anti-inflamation, anti-virus, anti-tumor and anti-aging, ***etc.***, with the anti-oxidative effect being the basis of the above properties. Nowadays, polysaccharides from more than a hundred Chinese herbal drugs including ***Lycium chinensis***, ***Coriolus versicolor***, ***Ganoderma lucidum***, garlic, ***Radix astragali***, ***Cordyceps sinensis***, ***gingko***, and ***Notoginseng***, ***etc.***, have been proved to have an anti-oxidant effect (Xin and Liu, 2000).

The cardiovascular effects of cardiac glycoside containing medicinal herbs were detected by traditional Chinese physicians at the beginning of the first century, and were proved to have potential inotropic and electrophysiological actions (Lu, 1987). ***Salvia miltiorrhiza***, ***Panax notoginseng***, hawthorn and ***Polygonum multiflorum***

Thunb are four medicinal herbs commonly used in traditional Chinese medicine and have previously been shown to provide cardiovascular protection and to be physiologically active on human vascular endothelial cells. The actions of *Polygonum multiflorum* Thunb and hawthorn to reduce apoptosis, and of *Salvia miltiorrhiza* and *Panax notoginseng* to inhibit the adhesion molecule expression may help protect the endothelial function and inhibit atherogenesis (Ling et al., 2008). *Radix Salviae miltiorrhizae* is officially listed in the *Chinese Pharmacopoeia* used for angina pectoris, and has been tested in clinical trials of ischemic diseases such as angina, heart attack and stroke (Xu et al., 2007). Experiments on myocardial ischemia-reperfusion injury in the isolated rat hearts illustrated the cardioprotective effects of purified *Salvia miltiorrhiza extract* perfused at a constant flow of 7-9 mL/min via the aorta (Chang et al., 2006b). Therapeutic treatment with salvianolic acids significantly reduced doxorubicin-induced toxicity, including elevation of body weight and the heart weight/tibia length ratio, decrease of CPK, improvement of electrocardiogram and heart vacuolation (Jiang et al., 2008).

Saponins are an important class of natural products with bioactivity. Saponins are composed of dioscingenin, glucose, uronic acid, and other organic acids. In the saponin molecule, there are many hydroxide radicals with big polarity. Furthermore, saponins usually share common physicochemical properties and similar bioactivities, such as an anti-platelet aggregation effect. Recent studies showed that saponins commonly have significant anti-oxidant effect, playing an important role in protection against many pathophysiological phenomena including senility, atherosclerosis, and ischemia-reperfusion injury (Xu et al., 2004). The cardioprotective effect of saponins rest on protection from myocardial damage caused by chemical or physical injury. For example, *astragaloside* can protect cultured neonatal rat myocytes from damage caused by free radicals and mitomycin C, whereas gypenosides can protect the contractility of the endotoxin-shocked guinea pig papillary muscle and rat myocardium. *Sasanguasaponin* can improve myocardial contractility, decrease the production of CPK and myocardial calcium content, and enhance cellular Na^+-K^+-ATPase and mitochondrial Ca^+-ATPase activities (Fan and Liao, 2003).

Flavonoids regulate cardiovascular function by way of their general characters of anti-oxidation and inflammatory inhibition. As bioflavonoids commonly contain active phenolic hydroxy group, they have good anti-oxidant property. Flavonoids can inhibit the oxidative modification of low density lipoprotein induced by Fe^{2+} and Cu^{2+}, and reduce the production of oxidized low density lipoprotein. They can also increase myocardial SOD and GSH-Px activities, decrease the capillary brittleness and permeability, and improve the microcirculation and rheology. Flavonoids may have an inhibitory effect on the expression of the adhering receptors. Its anti-inflammatory property may be associated with the inhibition of lipoxygenase during the biosynthesis of prostaglandin (Lan et al. 2005).

Alkaloids are widely distributed in the plant kingdom, in the families of *Dicotyledoneae*, such as *Ranunculaceae*, *Menispermaceae*, *Papaveraceae*, *Solanaceae*, *Apocynaceae* , and *Rutaceae*, etc., and *Monocotyledoneae* and lower plants as well. Alkaloids are always strongly active, being major active ingredients of Chinese herbal medicine (Feng and Shang, 2009).

The main pharmaceutical applications of polysaccharides are improvement of immunity, those of phenolic compounds are anti-senility while those of alkaloids are anti-tumor, inhibition of cardiovascular and digestive systems, and as an analgesic and an antipyretic. Left ventricular function improvement, isotropic effect, and free radical scavenging and anti-oxidant activities have been thought to be what the alkaloids contribute to myocardial preservation (Feng and Shang, 2009). Alkaloids may also inhibit platelet aggregation of the rabbit, decrease the myocardial contractility of the rabbit and guinea pig, reduce blood pressure and inhibit respiration. Some alkaloids showed a muscarinic effect and a nicotinic excitation (Yan et al., 2000).

Chinese medicinal monomers, such as *Ligustrazine* (Zhou, 2000), *Radix angelica sinensis* (Zhou, 2000), *Puerarin* (Deng et al., 2005), and Allicin (Li et al., 2001b), *etc*., may realize their cardioprotective effects by increasing plasma endothelin level, and decreasing the NO production. However, some monomers may show two-way regulations on the NO production according to their impact positions, dosage, concentration, and duration of action. For instance, *Ligustrazine* may induce the expression of NOS mRNA in oxygen-glucose deprivation myocytes, and increase NO production; meanwhile *Ligustrazine* can inhibit the expression of NOS and its genes and decrease NO production and therefore inhibit the formation of pulmonary hypertension and pulmonary vessel remodeling (Xu et al., 2001).

Calcium overload and free radicals are the main factors responsible for ischemia-reperfusion injury (Bagchi et al., 1997). *Panax notoginseng* saponins can improve the calcium pump activity of the sarcoplasmic reticulum membrane of the myocardium, and decrease the intracellular calcium. Allicin, liquorice, *Rhizoma chuanxiong*, and *Radix acanthopanacis senticosi* can function as calcium influx antagonists. The anti-oxidant property of Chinese herbal medicine display activities such as inhibiting the production of free radicals during ischemia-reperfusion, inhibiting lipid peroxidation induced by free radicals, protecting myocardial SOD activity, and counteracting damage by exogenous free radicals.

The ability to decrease myocyte apoptosis, and to effectively block the pathways of myocyte apoptosis have become valuable cardioprotective methods of Chinese medicine. *Astragalus* can inhibit myocyte apoptosis of rabbit during ischemia-reperfusion period, and so could puerarin when it was was used as suplement in cardioplegia. The mechanism of Egb761 to inhibit myocardial apoptosis may be probably associated with Ginkgolide B, which may promote endogenous anti-oxidant activity, prevent cellular membrane from damage from active oxygen, and alleviate calcium overload by counteracting platelet-activating factor and inhibiting lipid peroxidation caused by free radicals. Moreover, TNF-α may play an important part during the activation of the neutrophilic granulocytes. By this way, vascualr dysfunction and myocardial damage develop. Despite the appearance of many cytokines after myocardial ischemia, elevation of the TNF-α expression can only be apparent during reperfusion (Hansson, 1993; Herskowitz et al., 1995). In addition, IL-6 and -1 may impact on the myocytes and vascular endothelial cells, inducing the production of ICAM and prompting the adherence of the neutrophils and further ischemia-reperfusion injury. Puerarin can inhibit the increase of IL-6 secretion and oversecretion of IL-6 by hypoxic myocardium (Zhu et al. 2001).

In cardiac surgery, intermittent infusion of cold cardioplegia remains the main cardioprotective method, by which the myocardial metabolic rate can be decreased and myocardial endurance to hypoxia increased. Clinical study illustrated that the crystalloid cardioplegic solution containing puerarine (2 mg/kg) led to much less lactate and MDA contents, CPK and CK-MB delivery, and much better myocardial ultrastructure in comparison to the control in cardiac surgical patients (Yue and Hu, 1996). Cardioplegic infusion with ginsenosides (80 mg/L) or panaxadiol saponins (40 mg/L) as a supplement in rat heterotopic cardiac abdominal transplantation model obtained a higher myocardial GSH-Px activity, and lower lipid hydroperoxide content and mitochondrial score relative to the control (Yuan et al., 2003). Liu et al. (1998) reported St. Thomas II cold cardioplegia containing ginsenosides 80 mg/L was used in a transplanted rat heart after global ischemia for 60 mins and reperfusion for 30 mins. The SOD activity in the myocardium treated with ginsenosides was significantly higher, whereas the MDA and oxygen free radicals in the myocardium were markedly lower than that of the control, illustrating that ginsenosides as a supplement of cardioplegia may decrease toxicity of oxygen free radicals. Infusion of St. Thomas's Hospital solution plus Egb761 2.5 mL/kg led to an insignificant changes of MDA content before, during and after aortic clamping, indicating that Egb761 markedly reduce the production of lipid peroxide during reperfusion, which may be associated with its natural anti-peroxidate property,

well-preserved myocardial energy and reduced production of hypoxanthine and xanthine (Deng and Yu, 1999).

In general, the classification of Chinese herbal medicine according to the main effective ingredients facilitated the expression of their functioning ways, which were proved to be structure-sensitive. Chinese herbal drugs play an important role in cardioprotection from many different mechanisms, with the most recent and important finding being the inhibition of apoptosis. Further studies on Chinese herbal medicine in cardioprotective mechanisms are needed in order to find alternative ways for the clinical management of ischemia-reperfusion injury.

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