Potential cardioprotective effects of *Ginseng* preparations

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Abstract: *Ginseng* has shown potential cardioprotective effects by way of anti-oxidative, anti-arrhythmic, calcium-channel antagonistic, anti-inflammatory and anti-apoptotic properties. The underlying mechanisms may also lie in certain complex signaling pathways. Clinical evidence seemed to be less convincing as the potential cardioprotective effects of *Ginseng* have been investigated by using combined preparations rather than by purified bioactive ingredients in most occasions. The exact actions of *Ginseng* verified by using its individual bioactive ingredients will be our future research work.

Keywords: herbal medicine; myocardial ischemia; myocardial reperfusion.

INTRODUCTION

Ginseng, with a scientific name of *Panax Ginseng* C. A. Mey., is a perennial herbaceous plant that belongs to the *Araliaceae* family. According to place of origin, it can be divided into Chinese, Korean and American *Ginsengs*. Chinese and Korean *Ginsengs* are jointly called Asian *Ginseng* (*Panax Ginseng*). According to the processing of traditional Chinese Medicine, it is categorized into *Red Ginseng*, mould *Red Ginseng*, dried fresh *Ginseng*, dry and whole *Radix Ginseng* and active *Ginseng*, *etc*. Ginsenosides from raw *Radix Ginseng*, composed of triterpenes saponins, are considered major bioactive ingredients of this product (Jia and Zhao, 2009). Pharmacological properties of *Ginseng* are multiple due to its various components, notably saponins and polysaccharides and polyacetylenic alcohols, pertinent to anti-cancer, anti-diabetes, immunoregulation and neuroprotection (Wee *et al*., 2011). Increasing evidences suggested cardiovascular effects of bioactive constitutes of *Ginseng* as anti-ischemic, anti-oxidantive, anti-arrhythmic, anti-hyperglycemic or calcium-channel antagonistic agents (Wang *et al*., 2009a). The underlying mechanisms have recently been well documented by Kim (Kim, 2012). Modern pharmacological studies have greatly developed as to *Ginseng* research. Over the years, there have been repeated trails trying to introduce Chinese medicine including the bioactive ingredients or compound preparations of *Ginseng* as supplements to cardioplegia in order to highlight the cardioprotective effects of *Ginseng* in open heart surgery. However, there has been scanty of steady clinical research on this aspect for conclusions, but increasing evidences show that *Ginseng* has cardioprotective and anti-hypertensive effects and attenuates ventricular hypertrophy and congestive heart failure. *Ginseng,* along with its active ingredients ginsenosides, was shown protective effects on experimental ischemia-reperfusion heart models. However, such efficacy has not been convinced by well-designed, randomized, controlled trials in clinical practice. Distinct bioactive ingredients of *Ginseng* have distinct pharmaceutical properties. Research that was conducted on *Ginseng* preparations could only reveal the cardiovascular effects in general but it seemed to be impractical and difficult to disclose those of the individual ginsenoside as for the technologies available in the current era (Karmazyn *et al*., 2011). The present article aims to make a brief review of cardioplegic application of *Ginseng* preparations based on the literature information.

Bioactive ingredients

Experiments proved *Ginseng* contains many bioactive ingredients including ginsenosides, polysaccharides and peptides, *etc*., which display different pharmaceutical properties. As one of the major bioactive ingredients, ginsenosides, most of which are Rb1, Rd, Re, Rg1 and Rg3, may function as anti-oxidant, anti-inflammatory, anti-apoptotic and immunostimulant agents (Xiang *et al*., 2008). Moreover, as many as 200 saponins were isolated from *Ginseng*, mostly from the roots and partly from other parts of the plants (Christensen, 2009). Each saponin may have different pharmacologic properties in relation to their different chemical structures (Kim, 2012).

Cardioprotective effects

Ginseng has shown potential cardioprotective upon diverse pharmaceutical properties including anti-oxidant, anti-arrhythmic, anti-inflammatory, anti-apoptotic and calcium-channel antagonistic properties (Zhou *et al*., 2004). The underlying mechanisms for cardio protection also included complex signaling pathways that have been convinced by distinct researches.

Anti-arrhythmia

Triterpenoid saponins of *Ginseng* preparations may inhibit myocardial contractility, showing a negative inotropic effect on isolated experimental heart models. Meanwhile, ginsenosides may prevent ischemia-

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reperfusion arrhythmias, lower the prevalence of epinephrine-induced arrhythmias (Maslov and Konkovskaia, 2009), and decrease duration and amplitude of action potentials of the myocardial cells (Maslov and Konkovskaia, 2009). Total saponins and panaxatriol may attenuate myocardial ischemia-reperfusion injury of isolated rat heart models by enhancing left ventricular function (Kim and Lee, 2010).

Myocaldial cell membrane protection

Ginsenoside Rg1 pretreatment may be associated with significantly reduced release of lactate dehydrogenase and increased myocardial cell contractility in a dose-dependent manner in experimental rat models (Zhu *et al*., 2009). In diabetic rats subject to 30-min regional myocardial ischemia followed by 120-min reperfusion, ginsenoside Rb1 pretreatment may reduce myocardial infarct size, plasma creatine kinase (CK) and lactate dehydrogenase (Xia *et al*., 2011). Perioperative administration with *Shenfu Injection* (参附注射液, a preparation of the extracts of *Red Ginseng* and *Radix Aconiti Carmichael, primarily composed of* ginsenosides compound) before the start of cardiopulmonary bypass in cardiac surgical patients resulted in remarkably decreased plasma lactate dehydrogenase and creatine kinase isoenzyme MB (CK-MB) activities, which were particularly lower during myocardial reperfusion than during ischemic period (Jiang *et al*., 2007; Wang *et al*., 2007).

Calcium-channel antagonism

It has been disclosed that ginsenosides inhibited calcium-channels. The triterpenoid saponins of *Ginseng* may attenuate myocardial ischemia-reperfusion injury, and myocardial isoproterenol- or adriamycin-toxic injuries, which have been proved by relevant studies of both *in vivo* and *in vitro*. Molecular studies demonstrated that triterpenoid saponins act as an ion-channel antagonist by interactions with potassium $_{(ATP)}$-channels, and calcium-channels as well as with nitric oxide (NO) synthase, protein kinases, and steroidal hormone receptors, *etc*. (Maslov and Konkovskaia, 2009). MTT assays revealed that pretreatment with saponins derived from *Red Ginseng* significantly improved the viability of $Na_2S_2O_4$ hypoxia-injured cardiomyocytes *in vitro*. LY294002, a phosphatidylinositol 3-kinase (PI3K) inhibitor, had no negative influence on the cardioprotective effect of the saponins derived from *Red Ginseng*. Flow cytometrical study displayed that the saponins significantly reduced the intracellular calcium overload induced by $Na_2S_2O_4$, and decreased cardiac troponin I levels as well (Li *et al*., 2012a). Large-conductance $K_{(Ca)}$-channels play a pivotal role in determining membrane potential and the vascular tone. Ginsenoside Re activates calcium-activated potassium-channels, which determines the membrane potential of the vascular smooth muscle cells, in a dose-dependent manner (Nakaya *et al*., 2007). Ginsenoside Rg1 may also reduce intracellular calcium level in addition to regulate intracellular oxygen free radicals (Zhu *et al*., 2009).

Anti-inflammation

Preparations containing Ginsenosides alleviated inflammatory reactions secondary to heart operations under cardiopulmonary bypass in the congenital heart defect patients (Xia *et al*., 2005). Ginsenoside Rb1 pretreatment attenuated myocardial necrosis and neutrophilic inflammation response (Xia *et al*., 2011). Ginsenoside Rg1 also suppressed autophagic process of the H9c2 cardiomyocytes from hypoxia-reoxygenation injury (Zhang *et al*., 2012). In addition, perioperative use of *Shenfu Injection* was associated with a decreased plasma endothelin and elevated prostaglandin I_2 levels in patients undergoing cardiac operation under cardiopulmonary bypass (Wang *et al*., 2007).

Antiapoptosis

Previous study has shown that ginsenoside Rb1 significantly inhibited cardiomyocyte apoptosis and reduced ischemia-reperfusion in rats (Guan *et al*., 2002). In ischemia-reperfusion rat heart model, Bcl-2 gene expressions were remarkably upregulated and apoptotic cardiomyocyte counts were significantly reduced in *Radix Ginseng Rubra* Group comparing with the control (Liu *et al*., 2000; Zeng *et al*., 2004). Ginsenoside Rb1 suppressed H_2O_2-induced apoptosis by inhibiting mitochondrial permeability transition and caspase-3 activity (Na *et al*., 2012). *Shenfu Injection* pretreatment protected hypoxia-reoxygenation-induced apoptosis in isolated neonatal rat cardiacmyocytes showing reduced caspases-3 and -7 activities and decreased Bcl-2 expressions in the hypoxia-reoxygenation injured cardiomyocytes (Wang *et al*., 2009b; Xiao et al., 2013).

Anti-oxidation

Anti-oxidant phytochemicals are present in plants, fruits and vegetables (Lee *et al*., 2005). The cardioprotective effect of ginsenoside Rb1 was associated with attenuated the production of intracellular reactive oxygen species and well-preserved mitochondrial membrane, exhibiting a scavenging potent for different free radicals. The increased JNK phosphorylation in H_2O_2-exposed embryonic chick cardiomyocytes was subsided by the pretreatment with ginsenoside Rb1 (Li et al., 2012b). Ginsenoside Rb1 suppressed H_2O_2-induced apoptosis by inhibiting mitochondrial permeability transition and caspase-3 activity (Na *et al*., 2012). The protective effect of ginsenoside Rg1 against left ventricular hypertrophy in rats was discovered to be mediated by way of endogenous NO generations (Deng *et al*., 2010). In myocardial ischemia-reperfusion injury rat model treated with ginsenoside Rb1, the malondialdehyde contents in the myocardium were significantly decreased and superoxide dismutase activity, prominently enhanced. Triterpenoid

saponins enhanced the tolerance of cardiomyocytes to oxidative stress *in vitro* (Maslov and Konkovskaia, 2009). The possible mechanisms were primarily investigated that Ginsenoside Rb1 may upregulate the NO contents and the expressions of endothelial nitric oxide synthase (eNOS). However, the protective effect of ginsenoside Rb1 may be suppressed by L-NG-Nitroarginine Methyl Ester (L-NAME), a selective inhibitor of NOS (Xia *et al*., 2011). Ginsenoside Rb1 may play an important role in regulating eNOS activation and inducing NO generation in the endothelial cells of human aorta (Yu *et al*., 2007). *In vitro* porcine coronary arteries, ginsenoside Rb1 attenuated homocysteine-induced endothelial dysfunction, substantial free radical generation and downregulated eNOS expression (Zhou *et al*., 2005).

Signaling pathway reactions

Ginseng may protect the myocardium from ischemia-reperfusion injury in rodents by glucocorticoid receptor/estrogen receptor/-mediated reperfusion injury salvage kinase (RISK) pathway via an eNOS-dependent mechanism (Zhou *et al*., 2011). Ginsenosides increased the tolerance to oxidative stress, which effects was proved to be NO synthesis of triterpene saponines on the isolated endothelial cells. The possible molecular mechanisms were considered interactions with steroid hormone receptors, proteinkinases, NO synthase, guanilyl cyclase, calcium-activated potassium-channels and calcium-channels (Maslov and Lishmanov, 2008). The channel-opening ginsenoside Re could be inhibited by the selective eNOS inhibitor L-N_5-(1-iminoethyl)ornithine (L-NIO), but not by the selective neuronal nitric oxide synthase inhibitor S-methyl-L-thiocitrulline (SMTC). The Akt inhibitor SH-6 (10 μmol), and the PI3-kinase inhibitor wortmannin, completely blocked activation of calcium-activated potassium-channels by ginsenoside Re. These phenomena demonstrated ginsenoside Re may activate calcium-activated potassium-channels by activating eNOS and may activate eNOS in a c-Src/PI3K/Akt-dependent mechanism (Maslov and Konkovskaia, 2009). The activation of eNOS may be accomplished through a nongenomic pathway, in which consequent activations of c-Src, phosphoinositide 3-kinase, Akt and eNOS could be initiated. However, ginsenoside Re did not participate the proliferative processes of androgen- and estrogen-responsive genes through a genomic pathway. Thus, ginsenoside Re may protect against ischemia-reperfusion injury as a specific antagonist through a series of receptors including androgen, estrogen and progesterone receptors in a nongenomic steroid pathway mechanism (Furukawa *et al*., 2006).

Experimental studies disclosed that in the rat model with monocrotaline-induced right ventricle hypertrophy, total ginsenosides protected against the myocardial hypertrophy with a probable mechanism of downreulating the expressions of calcineurin and its catalytic subunit CnA through extra cellular signal-regulated kinase (ERK)-1 and mitogen-activated protein kinase (MAPK) phosphatase-1 (MKP-1) pathways (Qin *et al*., 2008). In addition, compound K, a metabolite of ginsenosides, showed NO-mediated cardioprotection through the Akt/PI3K pathway (Tsutsumi *et al*., 2011).

Cardioplegic supplements

Shengmai Decoction 生脉饮 is a traditional Chinese medicinal formula for tonifying *qi* and *yin*. The perfect formula (*Shengmai Injection* 生脉注射液), split formula (*Shenmai Injection* 参麦注射液), single herb (*Ginseng*) and its monomers (ginsenoside) have been proved to be excellent cardioprotective agents for myocardial ischemia-reperfusion injury (Shao *et al*., 2001). *Shenfu Injection* 参附注射液 is a commonly clinically used preparation for the treatment of cardiovascular disease. The major bioactive ingredients are ginsenoside and *Aconitum* 乌头类 alkaloids. Both ingredients show potent capacities of scavenging oxygen free radicals against lipid peroxidation. Ginsenosides play a myocardial protective role by providing with energy substrates, enhancing prosphorylation at a substrate level, boosting adenosine triphosphate synthesis and protecting the entity of mitochondrial membranes by decreasing calcium ion influx of the ischemic myocardium as a calcium-channel antagonist (Wei and Shen, 2007). Total ginsenosides contain many bioactive ingredients such as ginsenosides Rb1 and Rg1 and Notoginsenoside R1, *etc*. Ginsenoside Rb1 is a calcium-channel antagonist, while Notoginsenoside R1 is a good granulocyte inducer. Thus, total ginsenoside can act in improving microcirculation, protecting against oxidative stress, blocking calcium ion influx and inhibiting inflammatory reactions (Wen *et al*., 1993). Combined use of total saponins of *Ophiopogan*, ginsenoside and *Glycyrrhizin* remarkably reduce autorhythmicity of the right atrial myocardium and excitability of the left trial myocardium, prolong the atrial functional refractory period of the isolated rat heart and prohibit the autorhythmicity and arrhythmia of the isolated papillary muscle (Chen *et al*., 2000). In an experiment, isolated rabbit hearts subjected to ischemia 45-min and reperfusion injury 40-min at 37°C were perfused with St. Thomas cardioplegia with different concentrations of *Shenfu Injection* (1%, 5%, 10% and 15%). The results revealed that cardioplegia with 1%-10% *Shenfu Injection* had better myocardial protection in terms of myocardial enzyme leakage, coronary flow and cardiac performances in comparison to the control, whereas *Shenfu Injection* at a higher concentration of 15% to cardioplegia did not show myocardial protection effects (Cao and Min, 2005). In addition, reduced myocardial damage was noted in terms of decreased CK-MB, mitochondral malondialdehyde and Ca^{2+} contents as well as Flameng scores in the 1%, 5% and 10% *Shenfu*

Injection Groups (Cao and Min, 2006). Experimental studies demonstrated that cardioplegia with supplemented Chinese herbal medicinal ingredients such as *Tanshinone*, total saponins of *Panax Ginseng* and *Panax Notoginseng* saponins attenuated myocardial ischemia-reperfusion injury (Wu, 2005). The introduction of *Ginseng* preparation into cardioplegia alleviated the mitochondrial structural damages in the experimental canine hearts subjected to ischemia-reperfusion injury (Yuan *et al*., 1998). With panaxadiol saponin from *Ginseng* 40 mg/L added into the cardioplegia, the calcium content in the cardiomyocytes of the transplanted heart, and serum CK and CK-MB activities of the recipient mice were signiciantly reduced (Jiang *et al*., 2001). When St. Thomas II cold cardioplegia containing ginsenosides 80 mg/L was used in the heterotopic heart transplantation model in Wistar rats subjected to 60-min global ischemia and 30-min reperfusion, superoxide dismutase activity of the ginsenosides-treated myocardium was significantly enhanced than that of the control, whereas the malondialdehyde content and amounts of oxygen free radicals in the ginsenosides-treated myocardium were markedly decreased than that of the control (Liu *et al*., 1998).

Summary

Purified ginsenosides are usually preferred instead of the whole *Ginseng* root (Kim, 2012). Majority of the *Ginseng* preparations that arre popularly used are actually still not isolated bioactive ingredients. It inevitably leads to a difficult evaluation in quantifying the pharmacological effects of the product. Even more, it was once criticized for a possible placebo effect (Pinna, 2012). Moreover, some authors found that Korean *Red Ginseng* may induce human leukemia cells to apotosis (Park *et al*., 2009). Nevertheless, a more pleasant effect was still found with Korean *Red Ginseng* (Pinna, 2012). Scattered studies have revealed the potential cardioprotective effects of *Ginseng* as a therapeutic agent or as a supplement to the cardioplegia. However, clinical evidence looked like less convincing due to the fact that the compound preparations are used in most occasions. Most probably, co-treatment with the other ingredients from the compound preparations was rather mandatory on the whole. For this reason, the exact actions of *Ginseng* remain to be verified by using its individual bioactive ingredients rather than by its compound preparations in future research work.

CONCLUSIONS

Cardioprotective effects of *Ginseng* have been good as a therapeutic agent or as a cardioplegic supplement by using some compound preparations in most occasions. *Ginseng* has shown diverse pharmaceutical properties including anti-oxidant, anti-arrhythmic, calcium-channel antagonistic, anti-inflammatory, and anti-apoptotic and calcium-channel antagonistic properties. The mechanisms underlying the functional diversity might be along a series of complex signaling pathways. The exact actions in terms of either suppression or induction of cellular apoptosis have to be figured out. The mechanisms of the individual bioactive ingredients of *Ginseng* should be investigated in future research work.

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