SCIENCE CHINA
Life Sciences

• REVIEW •

March 2016 Vol.59 No.3: 292–298
doi: 10.1007/s11427-016-5007-8

Roles and mechanisms of ginsenoside in cardiovascular diseases: progress and perspectives

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Received September 8, 2015; accepted November 4, 2015; published online January 20, 2016

Ginseng is among the oldest traditional Chinese medicinal herbs and is widely used in China and Southeast Asia. Over the past 50 years, considerable research has focused on the chemical constituents, pharmacological action, and clinical applications of ginseng. In this review, we examine the current state of research on ginseng, including the main active ingredient ginsenoside, its pharmacological effects on the cardiovascular system, and mechanisms of action. We focus on what is known of the effects of ginseng against atherosclerosis, arrhythmia, myocardial ischemia, and its inhibition of ventricular remodeling, providing a basis for expanding the clinical applications of ginseng.

ginseng, ginsenoside, cardiovascular disease, mechanisms

Citation: Sun, Y., Liu, Y., and Chen, K. (2016). Roles and mechanisms of ginsenoside on cardiovascular diseases: progress and perspectives. Sci China Life Sci 59, 292−298. doi: 10.1007/s11427-016-5007-8

INTRODUCTION

Ginseng (*Panax ginseng* C.A. Meyer) is a perennial herb originating from the Tertiary period with about 60 million years of history that has survived because of genetic variations incurred during the Quaternary glacial epoch. It is often referred to as a periglacial plant and living fossil, and enjoys a reputation as the King of Herbs. Each part of the ginseng plant—but particularly the root—has high medicinal value and is widely used in Asia. According to *Shennong's Herbal Classic*, ginseng is one of the popular medicines for nourishing the body and can be taken over a long term without causing harm. Ginseng is sweet, tepid after processing, and non-toxic, and has an anti-aging effect owing to its ability to tonify Qi; this has been described in Zhang Zhongjing's book *Treatise on Cold Pathogenic and Miscellaneous Diseases* ("*Shanghan Za Bing Lun*"), Li Shizhen's work *Compendium of Materia Medica* ("*Ben Cao Gang Mu*"), and a variety of books on herbal medicine since the Qing Dynasty. It is also known to reinforce vital energy, fortify the spleen to benefit the lungs, nourish fluids, calm the heart, tranquilize the mind, and so on.

In the last 50 years, there has been considerable research on the active ingredients, pharmacological effects, and clinical applications of ginseng. The academic monograph *Chemistry, Biological Activity and Pharmacokinetics of Panax ginseng Meyer* (Zhang, 2012) has been updated to version 2 and is widely influential. Ginseng has various physiological effects; it is known to reduce fatigue, improve immunity, slow aging, inhibit cancer metastasis, regulate blood sugar, protect liver and kidney functions, and has nootropic effects, with two-way regulation of the central nervous system (Zhang, 1995; Chu and Zhang, 2009).

Cardiovascular diseases account for a large percentage of disease-related deaths worldwide, and as such, the discovery of novel drugs or compounds among traditional herbal medicines that have cardiovascular protective effects is a focus of intense research (Hao et al., 2015; Yao et al.,

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2015). Research on the cardiovascular pharmacology of ginseng has aroused great interest among scholars in recent years. The present review discusses the research carried out over the past decade in China and elsewhere on the main active ingredient of ginseng (i.e., ginsenoside), its pharmacological effects on cardiovascular function, and the underlying mechanisms of action. We specifically focus on the cardiovascular properties of ginseng, including its anti-atherosclerotic, anti-arrhythmic, and anti-myocardial ischemic effects and its inhibitory effects on ventricular remodeling. This evidence can provide a basis for further research on ginseng and expand its clinical applications.

CHEMICAL COMPONENTS OF GINSENG

More than 300 compounds have been isolated from ginseng. These include ginsenoside, the main active ingredient and one of more than 50 saponin monomers that influence metabolism as well as immune, antioxidant, endocrine, and central nervous systems and are used in the treatment and prevention of cardiovascular diseases; as well as polysaccharides, amino acids, proteins, carbohydrates, vitamins, organic acids, trace elements, and flavonoids.

Ginsenoside is a glycoside formed by removal of a water molecule from the hemiacetal hydroxyl of a sugar molecule and a hydroxyl from non-carbohydrate compounds. Ginsenoside differs from other saponins in terms of the ring structure of sapogenin. Ginsenosides can be classified into oleanolic acid, protopanaxadiol, and protopanaxatriol types based on the parent ring structure (Bai et al., 2014; Kim et al., 2015) (Figure 1 and Table 1).

CARDIOVASCULAR PHARMACOLOGICAL EFFECTS OF GINSENOSIDE AND MECHANISMS OF ACTION

Anti-atherosclerotic effects and protection of the vascular endothelium

Coronary heart disease is among the most common diseases and is caused by atherosclerosis (AS)-induced endothelial dysfunction leading to systemic organ disease (An et al.,

Table 1 Classification of ginsenosides

Subtype	Ginsenoside
Protopanaxadiol (PPD) type	Ra (1,2,3)
	Rb (1,2,3)
	Rc
	Rd
	$Rg3^+$
	$Rh2^+$
	F2
	Compound K
Oleanolic acid type	Ro
	Rh3
	Ri
Protopanaxatriol (PPT) type	Rg1
	Rg2
	Re
	Rf
	Rh1
	F1

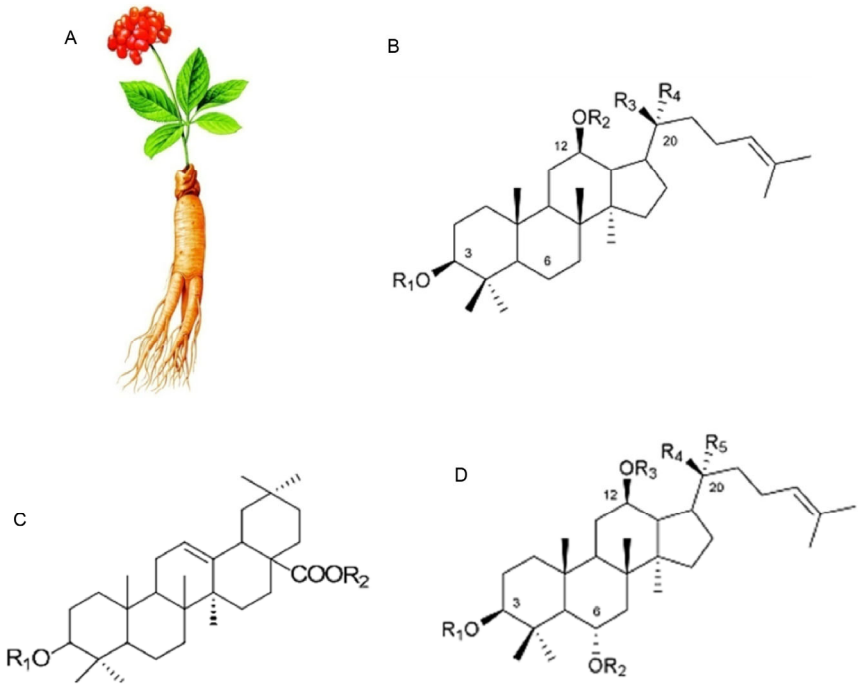

Figure 1 *Panax ginseng* C.A. Meyer plant and chemical structures of ginsenoside subtypes. A, Illustration of *Panax ginseng* C.A. Meyer. B–D, Chemical structures of protopanaxadiol-type (B), oleanolic acid-type (C), and protopanaxatriol-type (D).

2014; Zhang and Dong, 2014), which is associated with a high rate of morbidity and mortality. Risk factors for coronary AS include dyslipidemia, hyperglycemia, hypertension, and platelet aggregation and activation.

Oxidized low-density lipoprotein (oxLDL) inhibits lactate dehydrogenase (LDH) activity, decreases endothelial nitric oxide synthase (NOS) expression, and modulates tissue-type plasminogen activator and plasminogen activator inhibitor 1 (PAI-1) activities. Studies on human umbilical vein endothelial cells (HUVECs) pretreated for 24 h with a high dose of ginsenoside Rb1 (10 mg mL^{-1}) have reported an inhibition of oxLDL and consequent protection of endothelial cells (He et al., 2007). Hyperlipidemic rats fed ginsenoside Rh2 (200 mg kg^{-1} d^{-1}) for 11 weeks showed reduced serum LDL-C and total cholesterol (TC) levels and increased serum NO and superoxide dismutase activities. Rh2 also decreased malondialdehyde levels, reduced lipid peroxidation, enhanced oxygen free radical scavenging, and stabilized cell membranes, thereby protecting endothelial cells via these anti-AS effects (Kong et al., 2010). Similarly, hyperlipidemic rats treated with ginsenoside Rb (50–200 mg kg^{-1} d^{-1}) for 12 d showed decreased serum TC, triglyceride (TG), and LDL-C levels and increased HDL-C level, suggesting that Rb enhanced cholesterol transport from peripheral tissues to the liver, which in turn reduced cholesterol accumulation and prevented endothelial cell damage and AS (Zhang et al., 2004). In a rat carotid artery injury model, ginsenoside Rg1 improved tissue damage caused by aortic injury and neointimal thickening, suggesting that it can inhibit neointimal hyperplasia, possibly by reducing oxidative stress and stimulating NOS expression and NO production (Gao et al., 2012). Ginsenosides have also been shown to inhibit nuclear factor κB signaling (Ruan et al., 2004) by suppressing lipopolysaccharide-induced PAI-1 expression, promoting fibrinolysis, and preventing thrombosis in HUVECs. In a spontaneously hypertensive rat model, Rb1 reduced blood pressure at high (60 mg kg^{-1}) and low (30 mg kg^{-1}) doses over a 12-week period, possibly via regulation of the balance between helper T17 and regulatory T cells (Chen et al., 2014). Rats continuously treated with ginsenoside Rg2 at low (2.5 mg kg^{-1}), medium (5.0 mg kg^{-1}), or high doses (10 mg kg^{-1}) for 3 d exhibited prolonged thrombosis time and a decrease in adenosine diphosphate (ADP)-induced platelet aggregation (Tian et al., 2009). Similarly, in a rat model of acute blood stasis in which three doses of Rb (25, 50, and 100 mg kg^{-1}) were continuously administered for 7 d, blood viscosity, platelet aggregation, and blood rheology were improved, which prevented high-viscosity conditions in the coronary artery during acute myocardial infarction, thrombosis formation, and the occurrence and development of AS (He et al., 2007). Rg1 has also been shown to inhibit platelet aggregation and activation induced by thrombin, ADP, collagen, and the thromboxane analog U46619, likely via suppression of the extracellular signal regulated kinase (ERK) signaling pathway. An inhibitory effect on thrombus formation *in vivo* has also been demonstrated (Zhou et al., 2014). Ginsenoside Rp1 was found to inhibit platelet activation and thrombosis induced by collagen, which may be related to vasodilator-stimulated phosphoprotein activation and inhibition of ERK2 and p38 mitogen-activated protein kinase pathways (Endale et al., 2012).

Anti-arrhythmic effects

Current anti-arrhythmia drugs have the side effect of aggravating arrhythmias, prompting researchers to seek out alternative agents from herbal medicine. Ginsenosides can block ion channels, suggesting that they can be used to modulate arrhythmia (Wang et al., 2004). Three types of Ca^{2+} channel exist on the myocardial cell membrane: B background channels, and L- and T-type voltage-dependent channels. The L-type channel is the main conduit of intracellular Ca^{2+} during cell excitation.

Ginsenoside Rb1 treatment was found to block Ca^{2+} currents in a dose-dependent manner at concentrations of 100–400 mol L^{-1} in cardiomyocytes isolated from reverse-perfused guinea pig hearts using a whole-cell voltage clamp technique (Zeng et al., 1997). In another study using isolated rat ventricular myocytes perfused with Rb1 (40 μmol L^{-1}), L-type Ca^{2+} currents and transient outward K^+ currents were reduced without any alteration in channel kinetics (Pei et al., 2011). Ginsenoside Re administered at three doses (i.e., 5, 10, or 20 mg kg^{-1}) converted a triggered ventricular arrhythmia into a normal sinus rhythm in a rabbit isoproterenol-induced arrhythmia model, an effect that was dose-dependent. The effects of ginsenoside on hemodynamics are negatively related to dosage (Chen et al., 2009); ginseng stem leaf saponins had dose-dependent antagonistic effects on chloroform-induced mouse ventricular cardiac arrhythmia and prevented aconitine-induced ventricular arrhythmia. Chloroform improved myocardial cell self-regulation linked to Ca^{2+} influx (Tang et al., 2009). Ginseng stem leaf saponins were also found to suppress aconitine-induced rat ventricular cardiac arrhythmia, possibly by modulating Na^+ channel function (Xiao et al., 2013). Ginsenoside Re (10 or 100 mol L^{-1}) has been shown to exert anti-arrhythmic effects by inhibiting currents from ventricular voltage-dependent Na^+, transient outward K^+, and inward rectifier K^+ channels (Meng et al., 2013). In mice with toad venom-induced arrhythmia, 40 mg kg^{-1} total ginsenoside administration reduced the width of the QRS complex and increased T-wave amplitude, thereby diminishing the arrhythmia and prolonging survival (Lu et al., 2012).

Protective effects of ginsenosides against myocardial ischemia

In a Langendorff isolated heart model of ischemia-reperfusion, 40–160 mg L^{-1} ginsenoside pre-treatment and

80 mg L^{-1} post-treatment had a protective effect against myocardial ischemia-reperfusion injury in rats, with greater effects observed with 80 mg L^{-1} pre- and post-treatment doses (Li et al., 2005). Administration of total ginsenoside also improved myocardial ischemia-reperfusion coronary flow in a dose-dependent manner, which was likely associated with activation of the phosphoinositide 3-kinase/Akt-endothelial (e) NOS pathway and increased NO release (Yi et al., 2010). In addition, ischemic ventricular myocyte Ca^{2+} ion channels and Ca^{2+} currents were inhibited in a dose-dependent manner by Rb1 (100–400 μmol L^{-1}) (Zhang et al., 2007). Application of various doses of Rb1 in a H_2O_2-induced myocardial injury model had an anti-apoptotic effect via inhibition of lipid peroxidation and suppression of intracellular Ca^{2+} overload (Xu et al., 2005) and reactive oxygen species (ROS) production, which reduced oxidative damage and preserved mitochondrial function (Wen et al., 2010). Rb1 was also found to inhibit ROS-induced c-Jun N-terminal kinase (JNK) activation (Li et al., 2012) and ERK signaling (Yang et al., 2014). Re and Rg1 had protective effects on ^{60}Co irradiation-induced cardiomyocyte apoptosis that were exerted via attenuation of caspase 3 and B cell lymphoma (Bcl)-2-associated X protein (bax) expression and JNK/p38 signaling (Wu and Liu, 2008).

Administration of various doses of Rg1 promoted the formation of coronary artery collaterals in a rat acute myocardial infarction model, which may be associated with the upregulation of vascular endothelial growth factor expression and stimulation of angiogenesis (Zhang et al., 2009, 2013; Jin et al., 2007). In a rat coronary artery ligation-induced ischemia-reperfusion model, Rb1 (4 mg kg^{-1}) suppressed myocardial cell apoptosis (Zhang et al., 2001). Ginsenoside Rg3 (60 mg kg^{-1}) was also shown to have a protective effect on the myocardium via Akt/eNOS signaling and modulation of the Bcl-2/Bax ratio (Wang et al., 2015). In the same model, Rg1 (1–4 mg kg^{-1}) administered to guinea pigs in which acute myocardial ischemia was induced by pituitrin showed significant improvement in electrocardiogram readings as well as increased antioxidant enzyme activity, decreased oxidative damage from endothelial cell free radicals, and a reduction in myocardial cell membrane damage (Lai et al., 2011). Study in rats has shown that the effective dose of Re for protecting against heart ischemia-reperfusion injury in rats (determined by monitoring hemodynamic parameters such as perfusion pressure, aortic and coronary flow, cardiac output volume, and left ventricular pressure) was 100 μmol L^{-1} (Kyuhee, et al., 2013). Pretreatment of diabetic rats with Rb1 (40 mg kg^{-1} for 10 min) reduced the severity of myocardial ischemia-reperfusion injury, which was associated with increased NOS expression and NO release and suppression of the oxidative stress response (Xia et al., 2011).

Inhibition of ventricular remodeling

Ventricular remodeling refers to an increase in myocardial injury or ventricle load following alterations in cell size or shape, or ventricular wall thickness and structure. This phenomenon is generally associated with lesion repair and ventricular compensation, and is a secondary pathophysiological reaction to myocardial infarction. Ventricular remodeling can lead to deterioration of left ventricular systolic function, followed by congestive heart failure and death. Recent evidence suggests that ginsenoside is effective in mitigating this process.

In a rat model of pressure overload-induced left ventricular remodeling, continuous administration of Rb at 25–100 mg kg^{-1} d^{-1} for six weeks by gavage had a protective effect against ventricular remodeling, with improved left ventricular systolic and diastolic functions, enhanced antioxidant enzyme activity, reduced myocardial damage by free radicals and vasoconstrictors, and a restoration of plasma prostacyclin prime/thromboxane A_2 ratio (Wang et al., 2008). Left ventricular remodeling was reduced in rats with acute myocardial infarction by injection of Rb1 (2 mg kg^{-1}) for four weeks, which was likely associated with negative regulation of the renin-angiotensin system (Wang et al., 2006). In neonatal rat cardiac myocytes in which hypertrophy was induced by angiotensin II, Rb1 (50–200 μmol L^{-1}) suppressed the elevation in Ca^{2+} levels in a dose-dependent manner (Chen et al., 2008). Continuous application of Rb1 in a rat model of doxorubicin-induced heart failure reduced myocardial damage via modulation of connexin 43, which may be associated with the regulation of p21-activated kinase l/protein phosphatase 2A (Kong et al., 2013) and protein kinase RNA-like endoplasmic reticulum kinase signaling (Kong et al., 2013). Furthermore, Rb1 (70 mg kg^{-1} d^{-1}) used as preventive therapy for 7 months in cTnTR141W mice with dilated cardiomyopathy resulted in an improvement in cardiac function and mitigated ultrastructural damage to heart tissue by reversing the disordered arrangement of myocardial cells (Zhao et al., 2009). Continuous application of Rg1 (5 mg kg^{-1} d^{-1}) in rats with acute myocardial infarction increased the number of peripheral blood stem cells, stimulated stem cell homing to the infarcted myocardium, and induced myocardial regeneration, thereby reducing infarct size and ventricular remodeling (Yang et al., 2008). Rb1 was also shown to inhibit colchicine-induced right ventricular hypertrophy, which may be associated with suppression of calcineurin signaling (Jiang et al., 2007).

Other beneficial effects of ginsenosides

In addition to the effects described above, ginsenosides have demonstrated protective effects against cardiac toxicity during cardiac surgery. In one study in which ginsenoside Rd (30 mg kg^{-1}) followed by bupivacaine (2 mg kg^{-1} min^{-1}) was injected into rats for 30 min, a significant improvement

in blood oxygen level and saturation was observed, suggesting that ginsenoside pretreatment can increase survival rate in cases of cardiac toxicity caused by local anesthetics (Sun et al., 2010). A ginsenoside mixture (1.35 mg kg^{-1}) was reported to reduce gastrointestinal mucosal injury and inflammation caused by treatment of congenital heart disease in children (Xia et al., 2005). In addition, *in vitro* study has shown that the toxicity of aconitum to myocardial cells can be mitigated by co-administration with ginseng at a ratio of 1∶0.5 (Wang et al., 2015). Another study reported that Rg3 protects vascular endothelial cells via a mechanism involving estrogen receptor that is similar to the effects of 17-β-estradiol (Pan et al., 2014).

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Studies of the mechanisms of cardiovascular protection by ginseng have mostly focused on the action of ginsenosides (Figure 2), and there are a variety of patented Chinese medicines (ginseng preparations) that are used to treat cardiovascular diseases (Table 2). The pharmacological effects of other ginseng components are rarely addressed (Im and Nah, 2013). Ginseng holds great promise for the treatment of cardiovascular diseases, with many potential applications. Based on its cardiovascular pharmacological effects, clinicians should pay close attention to the combinations of drugs that are used with ginseng. There are reports of co-injecting ShenFu (a ginsenoside compound) with statins to treat non-ischemic heart failure (Zheng et al., 2010), dopamine to reduce recovery time of in cases of shock (Xu and Xu, 2012), metoprolol to treat coronary heart disease and heart failure (Yang and Lin, 2011), and trimetazidine to treat dilated cardiomyopathic heart failure (Yu et al., 2013). However, large, randomized, controlled, double blind clinical trials are needed to verify the clinical efficacy of these combinations, in addition to a more detailed analysis of the mechanisms of action. Despite the large number of products made from ginseng extract, there are no strict monitoring standards for their production, use, and quality control. The main method for extracting ginseng uses ethanol, followed by concentration and drying. However, due to the variety of purification methods adopted by different manufacturers,

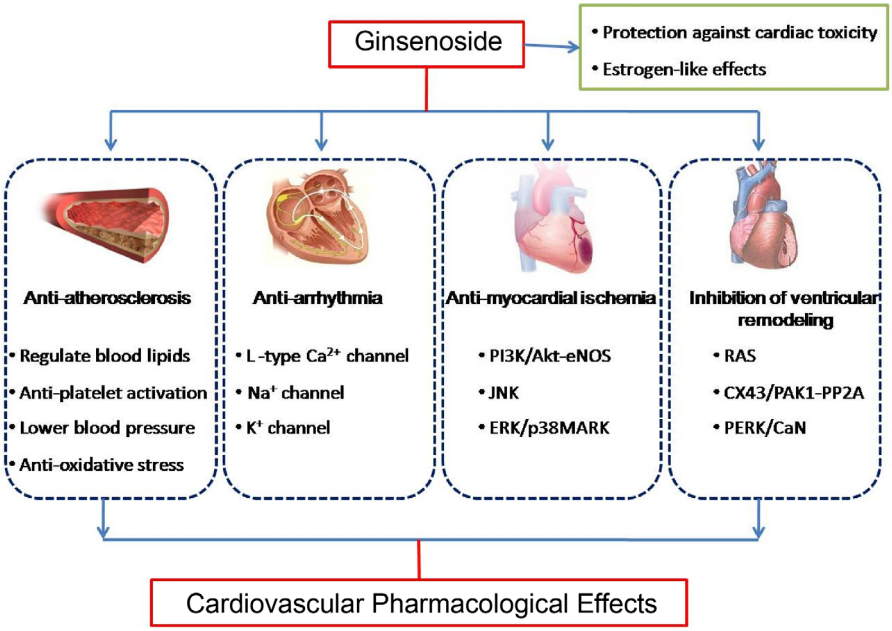

Figure 2 Putative mechanisms underlying cardiovascular protective effects of ginsenosides.

Table 2 Ingredients of frequently used patented Chinese medicines (ginseng preparations) for cardiovascular diseases

No.	Trade names of ginseng preparations	Ingredients	Types of ginsenoside	References
1	*Zhenyuan* capsule	Total saponins in the fruit of *Panax ginseng* C. A. Meyer	Ginsenoside Re	(Zhao, 2014)
2	*Xinyue* capsule	*Panax quinquefolium* saponin	Ginsenoside Rg1, Re, and Rb3	(Yang et al., 2013)
3	*Shenmai* injection	Red ginseng and *Radix ophiopogonis*	Ginsenoside Rg1 and Re	(Cao et al., 2011)
4	*Shengmai* injection	Red ginseng, *Radix ophiopogonis*, and *Schisandra chinensis*	Ginsenoside Rb1 and Rc	(Lu et al., 2011)
5	*Shenfu* injection	Red ginseng and *Aconitum carmichaelii*	Ginsenoside Rd, Rb1, Rb2, Rc, Rg1, and Ro	(He et al., 2014)

ginseng extracts differ significantly in terms of their properties, active ingredient content, and efficacy. Hence, to fully exploit the medicinal properties of ginseng and its extracts in the treatment of vascular diseases, production and monitoring systems must be improved. On the other hand, research on the possible toxicity of ginseng cannot be excluded; some studies have reported that Rb1 causes abnormalities in rat embryos (Chan, et al., 2003), which have aroused interest in exploring potential adverse effects of ginseng on development (Liu et al., 2005). Therefore, future research should not be confined to the benefits of ginseng and its preparations, and should be extended to a clarification of their mechanisms. With ongoing research on this versatile compound, more effective products will undoubtedly be developed for much-needed prevention and treatment of cardiovascular diseases.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

Acknowledgements *This work was supported by the National Natural Science Foundation of China (81403266) and the Sponsored Project from Advisor of Beijing Outstanding Doctorate Dissertation (20138450201).*

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