



‘Different Branches from the Same Root’: Similarity and Specificity of Five Saponins from *Panax Notoginseng* in Cardiovascular-Related Therapeutic Effects and Mechanisms

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Authors' contributions

This work was carried out in collaboration among all authors. Authors JL, XL and JD designated the topic. Authors ZW and KW performed the literature search. Authors JL and JC wrote the draft of the manuscript. Authors XL and JD revised the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Saponins are the major extracts of *Panax notoginseng*, which is one of the most commonly used herbal medicine in East Asia. Increasing evidences suggest that *Panax notoginseng* saponins (PNS) have various therapeutic effects on cardiovascular diseases. The therapeutic effects of PNS is through the complex combination of saponins. Notoginsenoside R1, ginsenosides Rb1, Rg1, Rd and Re are the major components of PNS, which have been studied thoroughly in recent years. In this review the authors summarize and compare the cardiovascular-related effects and mechanisms of these five saponins respectively. Anti-atherosclerosis, anti-inflammatory, anti-apoptosis are the most shared functions. But some of the functions are contradictory, such as

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GRb1 inhibit the endothelial tube formation and angiogenesis, while GRg1 promote the VEGF synthesis and angiogenic tube formation. Even GRg1 itself functions contradictory in angiogenesis. The comprehensive summary of the effects and mechanisms of saponins shed lights on the understanding of the diverse functions PNS exert, and lay groundwork for the development and utilization of saponins in cardiovascular diseases.

Keywords: *Panax notoginseng* saponins; saponins; cardiovascular; therapeutic effects; mechanisms.

1. INTRODUCTION

Panax notoginseng, also known as *sanqi*, *sanchi* or *tianqi* in East Asian (such as China, Japan and Korea), is one of the commonly used herbal medicine in Traditional Chinese medicine (TCM). According to the perspective of TCM, *Panax notoginseng* could exert the function of hemostasis and activating blood circulation to dissipate blood stasis. Normally hemostasis and activating blood circulation are contradictory, *Panax notoginseng* can adjust the balance in clinical use, which is familiar in genus *Panax*, and Ginseng is one of the representatives [1]. The chemical components of *Panax notoginseng* are complex, which up to 153 kinds. Saponins are the main pharmaceutical components of *Panax notoginseng* [2]. Such wide range of components makes the *Panax notoginseng* exert various functions. It's been reportedly that *Panax notoginseng* has the functions of anti-atherosclerosis, hemostasis, anti-coagulation, anti-oxidant, anti-inflammatory, neuroprotection, anti-tumor and so forth.

Though *Panax notoginseng* contains plenty kinds of saponins, the five saponins, including notoginsenoside R1 (7-10%), ginsenosides Rb1 (30-36%), Rg1 (20-40%), Rd (5-8.4%) and Re (3.9-6%), constitute up to 90% of total *Panax notoginseng* saponins (PNS) used in pharmacological experiments [3]. Different types of PNS are enriched in different parts of the *Panax notoginseng* plant, including root, rhizome and flower bud. Industrial extraction and isolation of saponins is by MeOH and high speed counter-current chromatography (HSCCC). Researches have demonstrated the partial and diverse functions of PNS in those five saponins. Since cardiovascular-related functions are the most frequently used and studied field of PNS in clinical practice and experimental researches, here we summarize and evaluate the cardiovascular-related researches of five saponins mentioned above respectively, hoping to gain insights into the variant functions of saponins and the similarities and specificities among them.

2. NOTOGINSENOSE R1

Of all the therapeutic effects Notoginsenoside R1 (NR1) exerts, including neuroprotection [4], Alzheimer's disease [5], inflammatory bowel disease [6] and osteoblastogenesis [7], cardiovascular protective effect attracts more attention in the research field. *In vivo* and *in vitro* experiments have demonstrated that cardiovascular protection could be achieved by multiple aspects, including anti-atherosclerosis, anti-inflammatory, anti-apoptosis, vascular protection and angiogenesis.

2.1 Anti-atherosclerosis

Atherosclerosis (AS) is pathological condition that lipids and fibrous lesions accumulate in the large arteries. Inflammation and oxidative stress are considered the risk factors and pathological mechanism of atherogenesis [8]. Animal experiment [9] has demonstrated that NR1 could attenuate the atherosclerotic lesion in ApoE^{-/-} mice and decrease the lipid deposition in the atherosclerotic lesions. Serum levels of glutathione (GSH) and superoxide dismutase (SOD) were increased, while serum levels of cholesterol (CHO), triglyceride (TG) and inflammatory cytokines were decreased, including interleukin (IL) -2, IL-6, tumor necrosis factor (TNF) - α and γ -interferon (IFN). Such anti-atherosclerosis effect might be attributed to the differentially expressed miRNAs which take part in the protective effect of NR1 in AS. The involvement of miRNA is a new perspective to study the functions of NR1 and PNS.

2.2 Anti-Inflammatory and Anti-Apoptosis

Both inflammatory and apoptosis play essential roles in AS. Various inflammatory molecules can activate T cells, macrophages and mast cells, leading to the secretion of inflammatory cytokines that reduce the stability of plaque [10]. And widespread apoptosis was detected from atherosclerotic lesions of native coronary vessels and saphenous vein grafts [11]. We have shown that NR1 could exert anti-atherosclerosis via

reducing inflammatory and apoptosis indicators [9]. Such effect might be achieved through these approaches: ①Activation of Peroxisome proliferator-activated receptor γ (PPAR γ): PPAR γ is a member of the nuclear receptor of ligand-activated transcriptional factors and plays key role in glucose, lipid metabolism [12], vascular endothelial function and AS. High level of oxidized low-density lipoprotein (ox-LDL) could induce the increase of IL-1 β and TNF- α , activate NF- κ B and Mitogen-activated protein kinases (MAPK). NR1 treatment could suppress ox-LDL induced inflammatory and apoptosis via activating PPAR γ , which subsequently inhibiting NF- κ B and MAPK activation [13]. ②Inhibition of endoplasmic reticulum stress (ERS): ERS-initiated apoptotic signaling has been implicated in ischemia/reperfusion (I/R) myocardium [14]. NR1 treatment can delay the onset of ERS by decreasing the protein expression levels of ERS-responsive proteins GRP78, P-PERK, ATF6 and IRE to achieve anti-apoptosis [15]. ③Activation of estrogen receptors (ER) α : Estrogen can significantly improve endothelium-dependent vasodilatation, promote and modulate vascular endothelial function, which may be protective against development of AS [16]. It is reportedly that endotoxin can induce the activation of NF- κ B, caspase-3 and inflammatory cytokines in cardiomyocytes. Treatment of NR1 could reduce endotoxin-induced cardiomyocyte inflammatory response and apoptosis through the activation of ER α , which enhances the activation and cardioprotection of estrogen [17].

2.3 Cardiomyocyte Protection

It's been proven that NR1 can protect the cardiomyocyte against I/R injuries through variant approaches [18,19]. The therapeutic mechanism may be concluded as follow: ①Anti-apoptosis: Apoptosis participate in I/R of cardiomyocytes and deteriorate the tissue damage. The anti-apoptosis effect of NR1 could function as myocardioprotection when pre-treats or post-treats the cardiomyocytes. ②Anti-oxidation: Oxidative stress response is considered one major damage mechanism of cardiomyocytes after I/R. Free radicals increase significantly after reperfusion. NR1 treatment reduces the activity of SOD, scavenges free radicals and increases the activity of antioxidant to achieve the anti-oxidation effect. ③Inhibition of Rho kinase (ROCK): ROCK has been known for

mediating actin filament stabilization and the generation of actin-myosin contractility. The deleterious role of ROCK has been implicated in the progression of cardiovascular diseases [20]. NR1 can inhibit the expression and activation of ROCK and restore the mitochondrial ATP synthase δ -subunits, thus prevent I/R-induced energy metabolism disorder [19].

2.4 Anti-hypertension, Vascular Protection and Angiogenesis

NR1 could exert anti-hypertension effect in rats, the underlying mechanism may involve the reduction of ERK expression and inhibition of ERK-related signal pathway, thus adjust the balance between vasoconstriction and vasodilation [21]. The anti-hypertension effect of NR1 is also implicated in hypertension-related lncRNA, that NR1 reduces the blood pressure of spontaneously hypertensive rats through induction of inducible nitric oxide synthase (iNOS) regulated by lncRNA AK094457 [22]. *In vivo* and *in vitro* experiments also showed the vascular protection and angiogenesis effect of NR1, the possible mechanism is activating the VEGF-KDR/Flk-1 and PI3K-Akt-eNOS signaling pathways to repair the blood vessel damage and proliferate endothelial cells [23].

3. GINSENOSES RB1

Ginsenosides Rb1 (GRb1) has been extensively studied and found to exert multiple biological functions including anti-inflammatory, anti-apoptosis and so forth [24]. Concerning cardiovascular-related functions, endothelial protection would be the major aspect.

The endothelial protection effect of GRb1 was observed in ox-LDL injured endothelial cells, with the inhibition of lactate dehydrogenase (LDH) activity, increase of nitric oxide (NO), endothelial nitric oxide synthase (eNOS), tissue-type plasminogen activator (t-PA) and decrease of plasminogen activator inhibitor-1 (PAI-1) [25]. The activation of eNOS and the increase of NO might be attributed to the GRb1 activated androgen receptor, the regulation of PI3kinase/Akt and MEK/ERK pathways [26] and the suppression of JNK phosphorylation [27]. The GRb1-induced NO generation can also inhibit the SA- β -gal activity and expression of PAI-1, which are two important senescence related biomarkers, protect endothelial cell from senescence [28].

The endothelial protection of GRb1 can also exhibit in the regulation of angiogenesis and proliferation of endothelial tissue. GRb1 can activate pigment epithelium-derived factor (PEDF) -one of the most potent natural inhibitor of angiogenesis- via stimulating ER β , to inhibit endothelial tube formation, thus exert the function of anti-angiogenesis, which is contrary to other saponins [29].

4. GINSENOSES RG1

The various functions of Ginsenosides Rg1 (GRg1) have also been studied thoroughly. The cardiovascular related functions of GRg1 can be summarized into two categories, myocardial protection and angiogenesis.

4.1 Myocardial Protection

Myocardial protection is vital and related to prognosis in cardiovascular diseases, especially in diseases that injure cardiomyocytes temporarily or permanently, such as myocardial ischemia, hypertension-induced myocardial remodeling and myocardial infarction. GRg1 can exert the myocardial protection through following aspects. ①Regulation of myocardial remodeling:

The anti-hypertension effect of GRg1 is controversial in different experiments, yet the protective effect of hypertension-induced myocardial remodeling is shared [30]. Such protective effect may be related to the upregulation of MMP-2, MMP-9 and associated signal pathways. GRg1 can also decrease the myocardial fibrosis and left ventricular hypertrophy, and preserve the cardiac function by potentially activating phosphor-Akt and inhibiting p38 MAPK signaling pathways [31].

②Inhibition of autophagy: Autophagy emerges as a new pathway responsible for maintaining cellular homeostasis via direct control of cell death and survival [32]. The balance of autophagy in diseases is sensitive, the level of autophagy may determine whether it is protective or detrimental in I/R [33]. Hypoxia/reoxygenation (H/R) -induced autophagy leads to cell injury, and GRg1 can inhibit the activation of AMPK α , promote the activation of mTOR, and decrease LC3B-2 and Beclin-1 to inhibit autophagosomal formation and apoptosis in cardiomyocytes [34].

4.2 Regulation of Angiogenesis

The GRg1-induced regulation of angiogenesis varies in different cardiovascular tissue and

pathological processes. In myocardial infarction rat, GRg1 treatment can stimulate angiogenesis in infarction area and increase the microvessel density via the excitation of mTOR receptor and hypoxia inducible factor-1 α (HIF-1 α) [35]. GRg1 can also stimulate HIF-1 α in human umbilical vein endothelial cells under normal cellular oxygen conditions to increase VEGF synthesis and angiogenic tube formation, exert the angiogenesis function [36]. As in TNF- α -induced pathological proliferation of human arterial smooth muscle cells, GRg1 can significantly inhibit the proliferation by the inactivation of ERK and PI3K/PKB pathways and modulation of cell-cycle proteins [37]. It is worth speculating that the angiogenesis regulation of GRg1 is dual-directional, similar to the function of hemostasis and activating blood circulation in *Panax notoginseng*.

The angiogenesis regulation of GRg1 was also studied in transcriptomic perspective. Three miRNAs, associated cytokines and pathways were screened out to be the action sites of GRg1, including miR-214/eNOS [38], miR-15b/VEGFR2 [39] and miR-23a/MET [40]. These results shed lights in new perspectives to understand the therapeutic mechanisms of saponins.

5. GINSENOSES RD

The studies of Ginsenosides Rd (GRd) concerning cardiovascular are relatively fewer, characterized by similarities and specificities compared to other saponins. GRd can prevent the development of AS by the inhibition of Ca²⁺ influx, the reduction of ox-LDL uptake and cholesterol accumulation in macrophages [41]. GRd can also protect the cardiomyocytes exposed to I/R and preserve the cardiac function via Akt/GSK-3 β signaling and inhibition of the mitochondria-dependent apoptotic pathway [42]. The functions of cardiovascular-related anti-inflammatory, anti-hypertension, anti-oxidation that other saponins possess have not been studied in GRd yet.

6. GINSENOSES RE

The cardiovascular-related functions of Ginsenosides Re (GRe) have been partially summarized before by Peng L et al. [43]. With the latest researches on GRe, the pharmacological effects of G-Re on the cardiovascular system include: ①Decreasing cardiac contractility by enhancing the release of

Table 1. The summary of five saponins' cardiovascular-related functions and mechanisms

		Atherosclerosis	Inflammatory	Apoptosis	Oxidation	Cardiomyocytes	Hypertension	Vascular protection and angiogenesis	Contractility and electrophysiology
Notoginsenoside R1	Regulation	Attenuate the atherosclerotic lesion	Reduce inflammatory indicators	Reduce inflammatory indicators		Protect against I/R	Anti-hypertension	Promote endothelial cells proliferation	
	Mechanism	Alter the AS-related miRNAs	1. Activate PPAR γ ; 2. Inhibit ERS; 3. Activate Era.	1. Activate PPAR γ ; 2. Inhibit ERS; 3. Activate Era.		1. Anti-apoptosis; 2. Anti-oxidation; 3. Inhibit ROCK	1. Inhibit ERK signal pathway; 2. Increase expression of lncRNA AK094457 to promote iNOS and NO expression	1. Activate VEGF-KDR/Flk-1 signal pathway; 2. Activate PI3K-Akt-eNOS signal pathway	
Ginsenosides Rb1	Regulation				Increase eNOS and NO			1. Protect injured endothelial cells; 2. Inhibit endothelial tube formation	
	Mechanism				1. Activate androgen receptor; 2. Regulate PI3kinase/Akt signal pathway; 3. Activate MEK/ERK signal			1. Activate eNOS and increase NO; 2. Suppress JNK phosphorylation; 3. Inhibit SA- β -gal activity and PAI-1; 4. Activate	

	Atherosclerosis	Inflammatory	Apoptosis	Oxidation	Cardiomyocytes	Hypertension	Vascular protection and angiogenesis	Contractility and electrophysiology
				pathway			PEDF	
Ginsenosides Rg1	Regulation				Protect cardiomyocytes		1. Stimulate angiogenesis in infarction area and HUVEC; 2. Inhibit TNF- α induced proliferation in HASMC	
	Mechanism				1. Regulate myocardial remodeling via MMP associated signal pathways, activating phosphor-Akt and inhibiting p38 MAPK signaling pathways; 2. Inhibit autophagy via suppress AMPK α , LC3B-2 and Beclin-1, promote mTOR		Stimulation: 1. Activate mTOR receptor and HIF-1 α ; 2. miR-214/eNOS, miR-15b/VEGFR2 and miR-23a/MET involvement. Suppression: Inactivate ERP and PI3K/PKB signal pathways	
Ginsenosides Rd	Regulation	Prevent development of AS			Protect against I/R			
	Mechanism	1. Inhibit Ca ²⁺ influx;			1. Active Akt/GSK-3 β signal			

		Atherosclerosis	Inflammatory	Apoptosis	Oxidation	Cardiomyocytes	Hypertension	Vascular protection and angiogenesis	Contractility and electrophysiology
		2. Reduce ox-LDL uptake and cholesterol accumulation in macrophages				pathway; 2. Inhibit the mitochondria-dependent apoptotic pathway			
Ginsenosides Re	Regulation				Anti-oxidation in cardiomyocytes			Promote HUVEC proliferation, migration and tube formation	1. Negative inotropic action; 2. Adjust electrophysiology
	Mechanism				1. Scavenge H ₂ O ₂ and hydroxyl radicals; 2. Increase endothelial Ca ²⁺ -activated K ⁺ outward currents			Not specified	1. Decrease cardiac contractility by increasing NO; 2. Suppress EMA by repairing SR Ca ²⁺ release

NO [44], and suppressing electromechanical alternans (EMA) by overcoming the impaired SR Ca^{2+} release [45]. ②Shortening the action potential duration (APD) and thereby prohibiting influx of excessive Ca^{2+} in ventricular myocytes [46]. The effect of GRe on cardiac electrophysiological properties was validated in later research [47], that treatment of G-Re before I/R induction significantly prevented the decrease in hemodynamic parameters (heart rate, perfusion pressure, aortic flow, coronary flow, and cardiac output), ameliorated the electrocardiographic abnormality, and inhibited TNF- α level. ③Anti-oxidation in cardiomyocytes: pretreatment with GRe can remarkably reduce cell death and protect the cardiomyocytes injured by both exogenous and endogenous oxidants. The protective effects may be attributed to scavenging H_2O_2 and hydroxyl radicals [48], and increased endothelial Ca^{2+} -activated K^+ outward currents which leads to stimulation of NO and vasodilation [49]. ④Angiogenesis: The angiogenetic effect of GRe was confirmed in human umbilical vein endothelial cells, with the proliferation, migration and tube formation significantly increased. Additionally, angiogenesis and tissue regeneration were detected in rat model received GRe [50].

7. CONCLUSIONS

Cardiovascular disease (CVD) is the leading cause of death worldwide. The medical and social burden of CVD has caused significant deleterious economic impact to both national economies and households [51]. The development of prevention and intervention for CVD is enormous and fast in the last decades. The utilization of complementary medicine and herbal extracts is drawing more and more attention in every aspects of medication, so does in CVD. *Panax notoginseng* is one of the representatives. With the continuous efforts, the major pharmaceutical components are elucidated, some of which have been developed into medication and perform well in clinical practice. In such circumstances, the thorough understanding of the pharmaceutical effects and mechanisms of the major extracts of *Panax notoginseng* is significantly important in the utilization and further development of medication.

Panax notoginseng have been demonstrated various functions in different aspects. As we

summarized above, the major components of *Panax notoginseng* exert similar and specific cardiovascular-related functions, some of which could be found in *Panax notoginseng*. Anti-atherosclerosis, anti-inflammatory, anti-apoptosis are the most shared functions. But some of the functions are contradictory, such as GRb1 inhibit the endothelial tube formation and angiogenesis, while GRg1 promote the VEGF synthesis and angiogenic tube formation. Even GRg1 itself functions contradictory in angiogenesis, stimulates angiogenesis in infarcted cardiomyocytes and inhibits in TNF- α -induced pathological proliferation of arterial smooth muscle cells. These results suggest that the functions of *Panax notoginseng* are not the simple addition of each saponins, and may explain the dual-directly regulation of *Panax notoginseng* in certain pathological process. The summary of five saponins' cardiovascular-related functions and mechanisms is listed in Table 1.

Literature searching indicated that most of the researches focused on single saponin or total PNS, the comparison between saponins in certain aspects of function is few. It is essential to elucidate the effects and mechanisms of different saponins on same pathological process, in cardiovascular diseases and other diseases. In that can we comprehensively understand the therapeutic effects of saponins and *Panax notoginseng*. Further investigations should also focus on the effects that have been demonstrated in other diseases and not been studied in cardiovascular diseases. This can expand the potential utilization of saponins. Medication development and clinical trials would be the future exploitation of saponins when we fully understand the advantages and scope of application.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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