

Perspective

Ginsenoside Rg1 Acts as a Glucocorticoid Receptor Ligand to Mediate Vasodilation through Nitric Oxide-cGMP Pathway

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Coronary Heart Disease (CHD) is the major cause of morbidity and mortality throughout the world [1]. Angina pectoris is caused by coronary blood flow that is insufficient to meet the oxygen demands of myocardium, leading to ischemia. Angina is present symptomatically in about 18% of CHD. Organic nitrates (and nitrites) have been widely used to alleviate or prevent angina pectoris for nearly one century. Nitroglycerin remains the mainstay of angina pectoris relief despite of its adverse effects and tolerance [2-6]. In Traditional Chinese Medicine, ginsenosides are used to relieve angina in CHD patients. Hundreds of randomized controlled trials (RCTs) reported claimed that ginsenoside formulas could relieve the symptoms of CHD, a meta-analysis of 18 eligible RCTs demonstrates moderate evidence that ginsenosides formulas are more effective than nitrates for angina patients [7]. Among the various ginsenosides extracted from ginseng, which component accounts for effects of ginsenoside formulas in relieving angina?

Asianginseng (*Panax ginseng* C.A.Meer) and Americanginseng (*Panax quinquefolius* L.) are the two most recognized ginseng botanicals around the world [8]. In both Asian ginseng and American ginseng, ginsenosides are the major active components [9]. Minor components include amino acid, peptides, and minerals. Ginsenosides are classified into two categories based on presence or absence of a carboxyl group at the C-6 position: protopanaxadiols (Rb1, Rb2, Rc and Rd) and protopanaxatriols (Rg1, Rg2, Re and Rf) [10]. Ginsenosides (except Ro) belong to a family of steroids named steroidal saponins [11,12]. Ginsenosides possess the four *trans*-ring rigid steroid skeleton, with a modified side chain at C-20. The classical steroid hormones have a truncated side chain or no side chain. Many steroids have a β -OH group at C-3; ginsenosides usually have a sugar residue attached to the same site. Ginsenoside Rg1 is among the most abundant and active ingredients in *panax ginseng*, it composed about 0.38% in root of *panax ginseng* [13]. Its molecular formula is $C_{42}H_{72}O_{14}$; molecular weight is 801.01268.

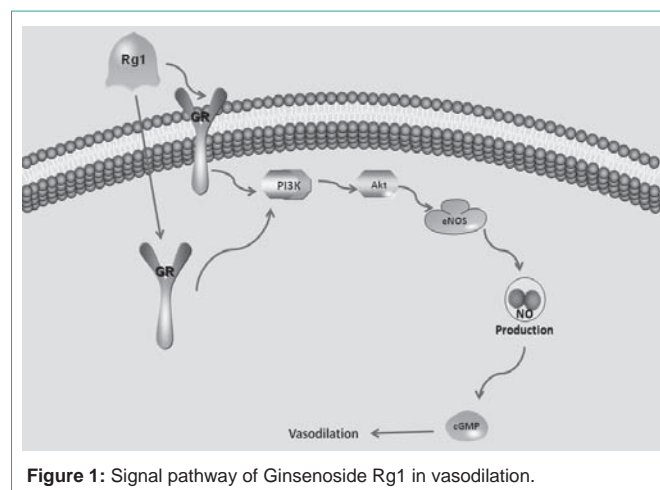


Figure 1: Signal pathway of Ginsenoside Rg1 in vasodilation.

The close connection between NO and ginsenoside Rg1 has increasingly been noted in recent years. Ginsenoside Rg1 has been demonstrated to trigger transcriptional activation of a glucocorticoid response element (GRE)-containing reporter gene, raising the possibility that Rg1 may activate the glucocorticoid receptor with specific affinity and activated a GRE-containing luciferase reporter gene, suggested Rg1 is a functional ligand of glucocorticoid receptor [14,15]. Rg1 competed for dexamethasone binding to glucocorticoid receptor with specific affinity and activated a GRE-containing luciferase reporter gene, suggested Rg1 is a functional ligand of glucocorticoid receptor [16]. Rg1 was presented to stimulate the NO formation in endothelial cells which accounts for the endothelium-dependent relaxation and production of cGMP in rat aorta [17]. In other studies, Glucocorticoids have been reported to activate the phosphatidylinositol-3 kinase (PI3K)/Akt pathway after binding to the glucocorticoid receptor [18]. The activated PI3K/Akt pathways leads to phosphorylation of endothelial nitric oxide synthase (eNOS) and increases the production of NO [19]. Rg1 could increase the phosphorylation of glucocorticoid receptor, PI3K, Akt/protein kinase B and eNOS leading to increase NO in human umbilical vein endothelial cell [20]. Rg1 induced endothelial-dependent vessel dilatation through the activation of NO by modulating the PI3K/Akt/eNOS pathway and L-arginine transport in endothelial cells [21]. The schematic signaling pathway of Rg1-mediated vasodilation was illustrated as figure 1. Animal studies showed Rg1 could reduce infarct volume in rat acute myocardial ischemia and infarction models [22]. Rg1 also resisted elevation of ECG T wave and ST segment on acute myocardial ischemia in guinea pigs.

Ginseng extract or ginsenoside formula occupied almost 70% of total Traditional Chinese Medicine used in the treatment of acute angina attack. When they are administrated by sublingual route, the effects can be achieved within several minutes. Rg1 may mediate

vasodilation through nitric oxide (NO)-cGMP pathway, increase blood supply to the heart muscle, and therefore alleviate angina pectoris. Ginsenoside Rg1 may have promising therapy perspective in the treatment of angina pectoris patients.

References

- Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation*. 2013; 127: e6-6e245.
- Marsh N, Marsh A. A short history of nitroglycerine and nitric oxide in pharmacology and physiology. *Clin Exp Pharmacol Physiol*. 2000; 27: 313-319.
- Katsuki S, Arnold W, Mittal C, Murad F. Stimulation of guanylate cyclase by sodium nitroprusside, nitroglycerin and nitric oxide in various tissue preparations and comparison to the effects of sodium azide and hydroxylamine. *J Cyclic Nucleotide Res*. 1977; 3: 23-35.
- Katsuki S, Arnold WP, Murad F. Effects of sodium nitroprusside, nitroglycerin, and sodium azide on levels of cyclic nucleotides and mechanical activity of various tissues. *J Cyclic Nucleotide Res*. 1977; 3: 239-247.
- Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhuri G. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. *Proc Natl Acad Sci U S A*. 1987; 84: 9265-9269.
- Ignarro LJ, Byrns RE, Buga GM, Wood KS. Endothelium-derived relaxing factor from pulmonary artery and vein possesses pharmacologic and chemical properties identical to those of nitric oxide radical. *Circ Res*. 1987; 61: 866-879.
- Jia Y, Zhang S, Huang F, Leung SW. Could ginseng-based medicines be better than nitrates in treating ischemic heart disease? A systematic review and meta-analysis of randomized controlled trials. *Complement Ther Med*. 2012; 20: 155-166.
- Qi LW, Wang CZ, Yuan CS. Ginsenosides from American ginseng: chemical and pharmacological diversity. *Phytochemistry*. 2011; 72: 689-699.
- Nah SY, Park HJ, McCleskey EW. A trace component of ginseng that inhibits Ca²⁺ channels through a pertussis toxin-sensitive G protein. *Proc Natl Acad Sci U S A*. 1995; 92: 8739-8743.
- Gillis CN. Panax ginseng pharmacology: a nitric oxide link? *Biochem Pharmacol*. 1997; 54: 1-8.
- Ota T, Fujikawa-yamamoto K, Zong ZP, Yamazaki M, Odashima S, Kitagawa I, et al. Plant-glycoside modulation of cell surface related to control of differentiation in cultured B16 melanoma cells. *Cancer Res*. 1987; 47: 3863-3867.
- Kim YS, Kim DS, Kim SI. Ginsenoside Rh2 and Rh3 induce differentiation of HL-60 cells into granulocytes: modulation of protein kinase C isoforms during differentiation by ginsenoside Rh2. *Int J Biochem Cell Biol*. 1998; 30: 327-338.
- Soldati F, Sticher O. HPLC separation and quantitative determination of ginsenosides from Panax ginseng, Panax quinquefolium and from ginseng drug preparations. 2nd communication. *Planta Med*. 1980; 39: 348-357.
- Kang SY, Lee KY, Lee SK. Ginsenoside-Rg1 regulates the induction of tyrosine aminotransferase gene transcription in rat hepatocyte cultures. *Biochem Biophys Res Commun*. 1994; 205: 1696-1701.
- Kim MY, Lee KY, Lee SK. Inductive effect of ginsenoside-Rg1 on tyrosine aminotransferase gene expression in rat primary hepatocyte cultures. *Biochem Mol Biol Int*. 1994; 34: 845-851.
- Lee YJ, Chung E, Lee KY, Lee YH, Huh B, Lee SK. Ginsenoside-Rg, one of the major active molecules from Panax ginseng, is a functional ligand of glucocorticoid receptor. *Mol Cell Endocrinol*. 1997; 133: 135-140.
- Kang SY, Schini-Kerth VB, Kim ND. Ginsenosides of the protopanaxatriol group cause endothelium-dependent relaxation in the rat aorta. *Life Sci*. 1995; 56: 1577-1586.
- Nogami H, Yamamoto N, Hiraoka Y, Aiso S, Sugimoto K, Yoshida S, et al. Rapid induction of the growth hormone gene transcription by glucocorticoids in vitro: possible involvement of membrane glucocorticoid receptors and phosphatidylinositol 3-kinase activation. *Journal of neuroendocrinology*. 2014; 26: 195-204.
- Nathan C, Xie QW. Nitric oxide synthases: roles, tolls, and controls. *Cell*. 1994; 78: 915-918.
- Leung KW, Cheng YK, Mak NK, Chan KK, Fan TP, Wong RN. Signaling pathway of ginsenoside-Rg1 leading to nitric oxide production in endothelial cells. *FEBS Lett*. 2006; 580: 3211-3216.
- Pan C, Huo Y, An X, Singh G, Chen M, Yang Z, et al. Panax notoginseng and its components decreased hypertension via stimulation of endothelial-dependent vessel dilatation. *Vascul Pharmacol*. 2012; 56: 150-158.
- Jin Y, Liu GN. Effects of ginsenoside Rg1 on angiogenesis and VEGF expression in rats with acute myocardial infarction. *Journal of China Medical University*. 2007; 36: 517-519.