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Review article

Pharmacological and medical applications of *Panax ginseng* and ginsenosides: a review for use in cardiovascular diseases

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ABSTRACT

Panax ginseng, also called Asian or Korean ginseng, has long been traditionally used in Korea and China to treat various diseases. The major active ingredients of *P. ginseng* are ginsenosides, which have been shown to have a variety of therapeutic effects, including antioxidation, anti-inflammatory, vasorelaxation, antiallergic, antidiabetic, and anticancer. To date, approximately 40 ginsenoside components have been reported. Current research is concentrating on using a single ginseng compound, one of the ginsenosides, instead of the total ginseng compounds, to determine the mechanisms of ginseng and ginsenosides. Recent *in vitro* and *in vivo* results show that ginseng has beneficial effects on cardiac and vascular diseases through efficacy, including antioxidation, control of vasomotor function, modulation of ion channels and signal transduction, improvement of lipid profiles, adjustment of blood pressure, improvement in cardiac function, and reduction in platelet adhesion. This review aims to provide valuable information on the traditional uses of ginseng and ginsenosides, their therapeutic applications in animal models and humans, and the pharmacological action of ginseng and ginsenosides.

1. Introduction

Panax ginseng is one of the most commonly greatly used species of ginseng. For thousands of years, this species, which is native to Korea, China, and Japan, has been an important cure in traditional medicine, where it has been used mainly as a remedy for spiritlessness and fatigue [1]. The name *panax* means "all healing" and stemmed from the traditional confidence that ginseng can cure all illness of the human body. The main active components in *P. ginseng* are ginsenosides, which are triterpene saponins. Most research on the pharmacological and medicinal functions of *P. ginseng* has focused on ginsenosides [2]. Among the ginseng species, *P. ginseng* (Korean ginseng), *Panax notoginseng* (Chinese ginseng), *Panax japonicum* (Japan ginseng), and *Panax quinquefolius* (American ginseng) are the most common. A lot of research has focused on individual ginsenosides instead of whole ginseng against many disease conditions [3–8]; among these ginsenosides, Rb_1, Rg_1, Rg_3, Re, and Rd are most often studied [8]. Cardiovascular disease is the major cause of morbidity and mortality and includes various diseases such as vascular disease, heart failure, coronary artery disease, cardiac ischemia, and hypertension [9]. Cardiac risk factors, such as cigarette smoking, increased low-density lipoprotein cholesterol, decreased level of high-density lipoprotein cholesterol, diabetes, and hypertension, are the main causes of cardiovascular disease [10]. Many researchers have shown that inflammation of blood vessels can result in atherosclerosis and coronary artery dysfunction [11]. Endothelial injury of blood vessels can be initiated by dangerous factors involved in cardiovascular disease [12]. Inflammation within the arterial wall is established by many cytokines, interleukins, and free radicals such as reactive oxygen species (ROS). Here, we review many research results on the roles and mechanisms of ginseng and ginsenosides to induce more studies into applications of ginseng and ginsenosides. The present review concentrated primarily on *P. ginseng*, but also considered studies on ginseng and ginsenosides

2. Ginsenosides are the pharmacologically active components in ginseng

Ginseng contains many active constituents, of which ginsenosides are very important. About 200 ginsenosides have been reported, including major ginsenosides (Rb_1, Rb_2, Rc, Rd, Re, Rg_1, etc.) and minor ginsenosides (Rg_3, Rh_1, Rh_2, etc.) [13]. By chemical structure, ginsenosides are classified into two major groups,

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protopanaxadiol (PD) and protopanaxatriol (PT), which share a four-ring hydrophobic steroid-like structure with sugar moieties, but differ in the carbohydrate moieties at C3, C6, and C20 (Fig. 1) [14,15]. To date, over 30 ginsenosides have been reported and classified into the two categories: (1) the 20(S)-PD (ginsenosides Rb_1, Rb_2, Rb_3, Rg_3, Rh_2, Rc, Rd, and Rs_1) and (2) the 20(S)-PT (ginsenosides Rg_1, Rg_2, Rh_1, Re, and Rf). The difference between PD and PT groups is the presence of a carboxyl group at the C6 position of PD [13,16].

Red ginseng, which results from the special preparation of ginseng, has an unusual saponin profile, with ginsenosides Ra_1, Ra_2, Ra_3, Rf_2, Rg_4, Rg_5, Rg_6, Rk_1, Rs_1, and Rs_2 likely being the results of stem transformation and deglycosylation of naturally generated ginsenosides [17–22]. These compounds can confirm the traditional knowledge that red ginseng is of higher pharmacological and medicinal functions than white ginseng [23]. Intestinal flora conditions change the relative composition of ginsenosides. Novel active compounds of ginseng formed by intestinal bacteria, such as compound K, might show more useful pharmacological and medical activities.

3. Ginsenosides modulate various ion channels

It was reported that ginsenoside Rd reversed the increase in store-operated Ca^{2+} channels or receptor-operated Ca^{2+} channels, but not voltage-dependent Ca^{2+} entry via a Ca^{2+} channel. This result suggests diminution of hypertensive remodeling after ginsenoside Rd administration [24]. Ginsenoside Re was shown to decrease heart rate, shorten the plateau phase of action potentials, and decrease P-wave amplitude, indicating blockade of slow Ca^{2+} channels mainly in the atria [25]. It was reported that ginseng depressed the L-type Ca^{2+} current in ventricular myocytes of guinea pig, and ginsenoside Re showed similar but weaker effects involving NO and the cyclic guanosine monophosphate pathway [26,27]. Ginsenoside Rg_3 decreased five subtypes of Ca^{2+} channel; L-, N-, P-, R-, and T-types [28,29]. Also, other ginsenosides have been shown to inhibit Ca^{2+} channels. For example, ginsenoside Rh_2 had a powerful inhibitory effect on L- and R-type Ca^{2+} channels, whereas CK strongly blocked only the T-type Ca^{2+} channel [28]. Ginseng treatment delayed K^+ current in ventricular myocytes of guinea pig, and ginsenoside Re demonstrated similar electrophysiological effects [26]. One study showed that NO induced by ginsenoside Re modulated cardiac K^+ channel activation and protected against ischemia-reperfusion injury in the heart [30].

4. Ginsenosides modulate cellular signal transduction

Although ginseng and ginsenosides have been widely used as pharmacological and medical substances, only a few studies have shown their effects on signal transduction pathways [31,32]. Ginsenoside Rg_1 can inhibit the C-Jun N-terminal kinase (JNK) signaling cascade through a protective effect against the phosphorylation of JNK [33]. In human astroglial cells, ginsenoside Rh_2 and compound K showed a primary inhibitory action on TNF-α–induced expression of adhesion molecule-1 by inhibiting TNF-α–induced phosphorylation of IκBα kinase [34]. Also, ginsenoside Rh_2 and compound K inhibited the phosphorylation and degradation of IκBα [34]. Furthermore, the same treatment with ginsenoside Rh_2 and compound K inhibited TNF-α–induced phosphorylation of MKK4 and suppressed the activation of the JNK-AP1 pathway.

5. Ginseng and ginsenosides improve antioxidant and blood circulation

Ginseng has antioxidative, vasorelaxation, anti-inflammatory, and anticancer activities [35]. In addition, ginseng is also widely used to address cardiovascular risk factors such as hypertension and hypercholesterolemia. Cardiac ischemia can be induced by myocardial damage through the production of ROS; however, ginseng and ginsenosides have been shown to improve the coronary blood flow [36]. In addition, an antioxidant role through Nrf2 and levels of antioxidant enzymes such as glutathione peroxidase and superoxide dismutase are increased by ginseng [37,38]. Ginsenosides inhibited myocardial injury through the increment of 6-keto-prostaglandin F1α and decreases of lipid peroxidation [39]. In addition, ginseng prevented ROS production through the stimulation of nitric oxide. Ginsenoside-Rb_1 and other ginsenosides blocked endothelial dysfunction induced by homocysteine through the inhibition of ROS production [40,41]. Ginsenoside Re is a strong antioxidant that conserves cardiomyocytes against oxidation via its free radical scavenging properties. Also, ginsenoside Re might play a primary role in an antioxidative effect to increase cardiomyocyte survival and cardiac contraction under cardiac ischemia [42,43]. These results suggest that ginsenoside Re has an antioxidant action, protecting cardiac cells from oxidative damage, and that these protective effects can be mostly attributed to scavenging of free radicals.

6. Ginsenosides ameliorate vascular function

It was well known that ginsenoside Rb_1 shows protective role on human umbilical vein endothelial cells [44]. Also, in such cells, a water extract of Korean ginseng induced angiogenesis through activation of phosphoinositol-3-kinase (PI3K)/Akt-dependent extracellular signal-regulated kinase 1/2 and endothelial nitric oxide synthase (eNOS) pathways [45]. Ginsenoside Re induced the activation of potassium channels in vascular smooth muscle cells [46]. *In vitro* extracts of *P. ginseng* and *P. notoginseng* increased

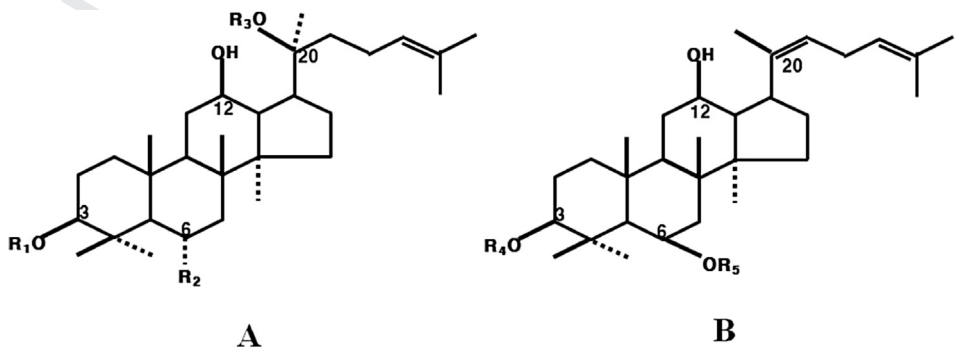

Fig. 1. Molecular structures of protopanaxadiol and protopanaxatriol of ginsenosides.