J Ginseng Res 38 (2014) 161–166

Contents lists available at ScienceDirect

Journal of Ginseng Research

journal homepage: http://www.ginsengres.org

Review article

A review on the medicinal potentials of ginseng and ginsenosides on cardiovascular diseases

Chang Ho Lee [1], Jong-Hoon Kim [2,*]

[1] Department of Pharmacology, College of Medicine, Hanyang University, Seoul, Korea
[2] Department of Veterinary Physiology, College of Veterinary Medicine, Biosafety Research Institute, Chonbuk National University, Jeonju, Korea

ARTICLE INFO

Article history:
Received 6 January 2014
Received in Revised form
12 March 2014
Accepted 18 March 2014
Available online 3 April 2014

Keywords:
antioxidant effect
cardiovascular diseases
lipid profile
myocardial protection
vasomotor tone

ABSTRACT

Ginseng is widely used for its promising healing and restorative properties as well as for its possible tonic effect in traditional medicine. Nowadays, many studies focus on purified individual ginsenoside, an important constituent in ginseng, and study its specific mechanism of action instead of whole-plant extracts on cardiovascular diseases (CVDs). Of the various ginsenosides, purified ginsenosides such as Rb1, Rg1, Rg3, Rh1, Re, and Rd are the most frequently studied. Although there are many reports on the molecular mechanisms and medical applications of ginsenosides in the treatment of CVDs, many concerns exist in their application. This review discusses current works on the countless pharmacological functions and the potential benefits of ginseng in the area of CVDs. Results: Both *in vitro* and *in vivo* results indicate that ginseng has potentially positive effects on heart disease through its various properties including antioxidation, reduced platelet adhesion, vasomotor regulation, improving lipid profiles, and influencing various ion channels. To date, approximately 40 ginsenosides have been identified, and each has a different mechanism of action owing to the differences in chemical structure. This review aims to present comprehensive information on the traditional uses, phytochemistry, and pharmacology of ginseng, especially in the control of hypertension and cardiovascular function. In addition, the review also provides an insight into the opportunities for future research and development on the biological activities of ginseng.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death globally. According to the World Health Organization, CVD was responsible for 30% of all deaths in 2005. Although typically considered a disease of developed countries, its incidence is increasing in the developing world as well. CVD usually stems from vascular dysfunction, for example, as a result of atherosclerosis, thrombosis, or high blood pressure, which then compromises organ function. Most notably, the heart and brain can be affected, as in myocardial infarction and stroke, respectively. In the past few decades, major improvements have been made in treating some types of CVD. However, new treatment options are urgently needed for all types of CVD. Moreover, improving diagnosis is crucial, because by detecting the early stages of disease, the focus of therapy could be shifted from treatment to prevention [1]. CVD is the leading cause of morbidity and mortality in millions of people around the world, which include a variety of diseases such as peripheral vascular disease, coronary artery disease, heart failure, dyslipidemias, and hypertension [2]. People of all races, age, and gender suffer commonly from these diseases. Heart failure, myocardial rupture, or arrhythmia is a result of myocardial necrosis following infarction [3]. Myocardial infarction and sudden death continue to remain as one of the leading causes of morbidity and mortality in many countries, despite vast advances in the past five decades. In addition, risk factors such as cigarette smoking,

* Corresponding author. Department of Veterinary Physiology, College of Veterinary Medicine, Biosafety Research Institute, Chonbuk National University, 664-14, 1ga, Duckjin-dong, Duckjin-gu, Jeonju, Jeollabuk-Do 561-756, Korea.
E-mail address: jhkim1@chonbuk.ac.kr (J.-H. Kim).

1226-8453/$ – see front matter Copyright © 2014, The Korean Society of Ginseng, Published by Elsevier. All rights reserved.
http://dx.doi.org/10.1016/j.jgr.2014.03.001

elevated low-density lipoprotein cholesterol, low levels of high-density lipoprotein cholesterol, diabetes mellitus, and hypertension are the primary causes of CVD [4]. Recent studies elucidate that vascular inflammation may also manifest in atherosclerosis and coronary artery disease [5]. Endothelial dysfunction has been stimulated by risk factors involved in CVD, such as expression of adhesion molecules by these dysfunctional endothelial cells, which promote the binding and influx of T cells and mast cells [6]. An inflammatory condition within the arterial wall is created by interleukins, cytokines, and reactive oxygen species (ROS) produced by white blood cells. Low-density lipoprotein is an atherogenic lipoprotein that accesses the subendothelial space and undergoes oxidative modification when trapped in the intercellular matrix [7].

Panax ginseng is a traditional herbal medicine that has been used therapeutically for more than 2000 years. It is the most valuable of all medicinal plants, especially in Korea, China, and Japan. The name *panax* means "all healing," and has possibly stemmed from traditional belief that the various properties of ginseng can heal all aspects of the illness encountered by the human body (i.e., it acts as a *panacea* for the human body). Among the ginseng species, Korean ginseng (*P. ginseng*), Chinese ginseng (*Panax notoginseng*), and American ginseng (*Panax quinquefolius*) are the most common throughout the world. Numerous studies focus on the research of individual ginsenosides instead of using whole ginseng extract against various diseases [8–13]. Of the various ginsenosides, Rb1, Rg1, Rg3, Re, and Rd are the most frequently studied [13].

This review describes the medicinal potentials of using ginseng and ginsenosides in the treatment of CVD. The review explores recent studies carried out to understand the mechanisms that lead to various diseases and discusses the implications of these advances for identifying new therapeutic targets and developing new therapeutic strategies, including the potential use of ginseng and its metabolite (i.e., ginsenosides) for treating CVD.

2. Efficacy of ginseng in improving circulation and antioxidant activity

Ginseng and ginsenosides have vasorelaxation, antioxidative, anti-inflammatory, and anticancer properties. In addition, ginsenosides have also shown to have an effect on the nervous system [14]. Moreover, ginseng has shown more benefit in individuals with diseases compared with healthy individuals [15–17]. In addition, a previous study supported its growing evidence for its indications in CVDs [12]. *P. ginseng* roots and extracts have been traditionally used by Koreans to renew the body and mind, and improve physical condition. Ginseng is also widely used in individuals with cardiovascular risk factors such as hypertension and hypercholesterolemia. Cardiac ischemia can cause myocardial injury that leads to the production of ROS, and in such cases, treatment with ginseng restores coronary blood flow to normal levels [18]. Alteration or loss of cellular function results in nonspecific damage to lipids, proteins, and DNA by ROS. The life span of animals bearing a tumor has gradually increased after ginseng treatment [19]. Oxidation-induced damage of erythrocyte membrane was reduced by ginsenosides Rg2 and Rh1 [20], and the energy metabolism and protection of the mitochondria have been effectively regulated by polysaccharides from *P. ginseng* [21]. Facilitation of antioxidant effect through Nrf2 and levels of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase were significantly increased by ginseng [22,23].

Ginsenosides protect from myocardial reperfusion injury by increasing 6-keto-prostaglandin F1α production and decreasing lipid peroxidation [24]. Rabbit pulmonary endothelium was protected from ROS toxicity by ginsenosides [8]. In addition, ginseng prevented ROS toxicity by stimulating nitric oxide (NO) production. Endothelial dysfunction was induced by homocysteine and human immunodeficiency virus protease inhibitors; however, these were successfully blocked by ginsenoside Rb1 and other ginsenosides by inhibiting the production of ROS [25,26]. Ginsenoside Re is a potent antioxidant that protects cardiomyocytes against oxidant-mediated injury. Such protection is, at least in part, mediated by its radical scavenging properties, especially for H_2O_2 and hydroxyl radicals. As a major constituent in ginseng extract, ginsenoside Re may play an important role in antioxidant actions to increase cardiomyocyte survival and contractile function during ischemia and reperfusion [27,28]. These results suggest that ginsenoside Re functions as an antioxidant, protecting cardiomyocytes from oxidant injury induced by both exogenous and endogenous oxidants, and that its protective effects may be mostly attributed to scavenging H_2O_2 and hydroxyl radicals.

3. Efficacy of ginseng in modulating vascular function

Interestingly, when glucose is attached to the 20th carbon of dammarane triterpene, such as ginsenosides Re, Rd, and R1, the ginsenosides acted as an antioxidant. By contrast, if no sugar moieties were attached to the 20th carbon of the ginsenosides such as Rg3, Rh2, and Rg2, the ginsenosides acted as a prooxidant. In ginsenosides such as Rh1, glucose is attached to the sixth carbon instead of the 20th, and in this case, the ginsenoside acts as an antioxidant only [29]. All these aggregated reports revealed that the prevention of ROS generation by ginseng may be an important milestone in the prevention of oxidative damage. Ginsenoside Rb1 has protective effects on human umbilical vein endothelial cells *in vitro* [30]. Water extract of Korean red ginseng stimulates angiogenesis by activating the phosphoinositol-3-kinase (PI3K)/Akt-dependent extracellular signal-regulated kinase 1/2 and endothelial nitric oxide synthase (eNOS) pathways in human umbilical vein endothelial cells [31]. Angiomodulatory and neurological effects are also shown by ginsenosides [32]. One study shows that potassium channels of vascular smooth muscle cells have been activated by ginsensoside Re through the PI3K/Akt and NO pathways [33]. Another study shows that ginsenoside Re has nongenomic effects in endothelial cells through the glucocorticoid receptor (GR) [34]. Capillary morphogenesis was attenuated by ginsenoside Rb1 [35]. Another *in vitro* study revealed the enhancement of vascular endothelial cell proliferation and migration by extracts of *P. ginseng* and *P. notoginseng* [36]. Saponin from *P. notoginseng* shows angiogenic effects on both human umbilical vein endothelial cells and in zebrafish models [37]. It is also reported that atherosclerotic lesions in apolipoprotein E (ApoE)-deficient mice and tumor necrosis factor-alpha-induced endothelial adhesion molecule expression have been reduced by *P. notoginseng* [38]. Production of NO was increased by ginsenoside Rg3 by increasing phosphorylation and expression of eNOS [39]. In human umbilical vein endothelial cells, fibroblast growth factor-induced angiogenesis was inhibited by compound K through the modulation of p38 mitogen-activated protein kinase (PK) and Akt [40]. The aforementioned reports propose that the saponin extracted from ginseng protects vascular endothelial cells through the NO-, Akt-, and GR-mediated signaling pathways. Effects of ginseng and ginsenosides have been sufficiently studied on the cardiovascular system. Through the production and release of NO, endothelium regulates blood vessel tone [41–43]. Production of NO has been stimulated by ginsenosides by a number of ways. It is reported that NO production in human aortic endothelial cells was induced by purified ginsenoside Rb1 [44]. Ginsenoside stimulates NO release in human umbilical vein endothelial cells by phosphorylation of GR, PI3K, Akt/PKB, and eNOS [45]. In isolated canine corpus cavernosum model, ginsenoside Rg3 induced vasodilation [46], which shows that arterial stiffness has been improved by Korean red ginseng and ginsenosides [47].