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Review article

Functional role of ginseng-derived compounds in cancer

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ABSTRACT

Ginseng is a natural product best known for its curative properties in diverse physiological processes such as cancer, neurodegenerative disorders, hypertension, and maintenance of hemostasis in the immune system. In previous decades, there have been some promising studies into the pharmacology and chemistry of ginseng components and the relationship between their structure and function. The emerging use of modified ginseng and development of new compounds from ginseng for clinical studies have been topics of study for many researchers. The present review deals with the anticancer, anti-inflammatory, antioxidant, and chemopreventive effects, and recent advances in microRNA technology related to red ginseng. The review also summarizes the current knowledge on the effect of ginsenosides in the treatment of cancer.

1. Introduction

Cancer is a global health problem that has shown an increase in incidence and mortality rates in recent years. Worldwide, the occurrence of cancer is on the rise because of the increase in population as well as risk factors like smoking, obesity, physical inactivity, and urbanization; the data published by GLOBOCON conclude that ~14.1 million new cancer cases and ~8.2 million deaths occurred worldwide in 2012 [1]. Tumor promotion is repeatedly accompanied by cellular, biochemical, and molecular events such as the generation of reactive oxygen species, depletion/suppression of antioxidant defense, acute inflammation followed by skin edema and hyperplasia, induction of cyclooxygenase (COX) activity, and increase in catalytic activity of ornithine decarboxylase and its messenger RNA (mRNA) expression [2,3]. Tumor promotion is closely related to inflammatory mechanisms that stimulate the proliferation of initiated cells; however, natural compounds isolated form medicinal plants possess extraordinary anti-inflammatory and anticarcinogenic activities. Currently, chemotherapy is the only standby for cancer therapy, which has several disadvantages like the development of chemoresistance. Moreover, cytotoxic agents are effective against cancer but they cause serious damage to normal cells causing severe adverse effects and complications, such as fatigue, pain, diarrhea, nausea, vomiting, and hair loss. These agents cannot be used for cancer treatment; therefore, there is an urgent need to develop a potent medication that is effective for cancer treatment without any adverse effects [4].

Natural compounds derived from plants have recently been gaining popularity because of their pharmacological and clinical effects in various diseases like cancer and neurodegenerative disorders. Therefore, there is a need to develop effective and reliable medication that can be pharmacologically as well as naturally accepted as a source of treating major disorders. Ginseng is the most reliable medicinal herb used in Asia and North America. Ginsenosides isolated form ginseng belongs to the family of steroids with a four trans-ring steroid skeleton divided into several groups, but there are two major functional groups based on their C6 position, namely: (1) protopanaxadoil (PPD) belongs to dammarane-type ginsenosides such as ginsenosides Ra1, Ra2, Ra3, Rb1, Rb2, and Rb3; (2) notoginsenoside R1, R2, Rs1, and Rs2; (3) quinquenoside R1; (4) malonylginsenoside Rb1, Rb2, Rc, and Rd (Fig. 1); and (5) protopanaxatrion (PPT) also belongs to dammarane-type ginsenosides which includes Re, Rf, Rg1, and notoginsenoside Rh1 (Fig. 1), while ocotillol and oleanane groups are the minor groups [5–7]. The new class of heat-processed

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A. Protopanaxatriol

Name	R1	R2	Formula
20(S)-G-Rb$_1$	Glc^2-Glc	Glc^6-Glc	$C_{54}H_{92}O_{23}$
20(S)-G-Rb$_2$	Glc^2-Glc	Glc^6-Arap	$C_{53}H_{90}O_{22}$
20(S)-G-Rc	Glc^2-Glc	Glc^6-Araf	$C_{53}H_{90}O_{22}$
20(S)-G-Rd	Glc^2-Glc	Glc	$C_{48}H_{82}O_{18}$
20(S)-G-Rg$_3$	Glc^2-Glc	OH	$C_{42}H_{72}O_{13}$
20(R)-G-Rh$_2$	Glc	OH	$C_{36}H_{62}O_8$

B. Protopanaxadiol

Name	R1	R2	Formula
20(S)-G-Rg$_1$	Glc	Glc	$C_{42}H_{72}O_{14}$
20(S)-G-Re	Glc^2-Rha	Glc	$C_{46}H_{82}O_{18}$

C. Oleanolic acid

Name	R	Formula
G-Ro	Glc A^2-Glc	$C_{48}H_{76}O_{19}$

D. Ocotillol

Name	R	Formula
F$_{11}$	Glc-Rha	$C_{42}H_{72}O_{14}$

Fig. 1. Classification and chemical structure of ginsenosides based on sugar attachments on the skeleton and R groups of ginsenosides. (A) Protopanaxatriol, (B) protopanaxadiol, (C) oleanolic acid, and (D) ocotillol.

Korean ginseng (steamed at 98−100°C for 2−3 h), sun ginseng (steamed at 120°C for 2−3 h), and black ginseng (repeatedly steamed and dried 9 times) appears to have decreased content of common ginsenosides (Rb1, Rc, Rd, Re, and Rg1) but comprises an array of ginsenosides that includes Rg5, Rk1, Rk2, Rk3, Rs4, Rs5, Rs6, and Rs7 [4,8,9]. Such changes in composition of ginsenosides give heat-processed ginseng its unique anticancer properties. Recently, a novel glycolipoprotein from *Panax ginseng*, known as gintonin (Fig. 2), was identified, which consists of a complex of lysophosphatidic acid (LPA) and ginseng proteins [10]. Gintonin consists of approximately 9.5% LPA and majorly consist of LPA in gintonin comprises of $C_{18:2}$ [11], which plays an important role in proliferation and migration of cells in vascular development and neurite reaction. LPA receptor-mediated cellular effects are coupled with brain development, angiogenesis, embryo implantation, spermatogenesis, and wound healing [12]. Gintonin is a potential ginseng compound with diverse molecular mechanisms and could be a breakthrough in pharmacological studies and development of novel drugs.

Ginsenosides have numerous pharmaceutical activities, such as enhancing cardiovascular health [13], stimulation of immune function [14], increasing resistance to stress [15,16], enhancing learning and memory [17], developing mental health, and social functioning in normal adults [18,19]. Ginsenosides also have shown strong chemoprotective and chemotherapeutic properties in a wide range of experimental studies both *in vitro* and *in vivo* [20,21]. Moreover, researchers have been interested in studying the role of microRNA (miRNA), which act as a group of small noncoding RNAs that regulate gene expression post-transcriptionally, and play an important role in regulating cellular mechanisms such as proliferation, differentiation, cell cycle, and apoptosis [22,23]. miRNAs appear to be important gene regulators and key players in carcinogenesis by acting as oncogenes or tumor suppressors [24]. Nonetheless, the focus has been directed towards novel antiangiogenic agents, and data obtained from microarray-based miRNA experiments show that ginsenoside Rg1 induces angiogenesis, which increases production of angiogenic factors, endothelial nitric oxide (NO) synthase [25], angiogenic receptors, and vascular endothelial growth factor receptor 2 in human umbilical vein endothelial cells [26]. The data suggest that miRNA-related gene expression plays an important role in ginsenoside-mediated angiomodulation.

There have been efforts to identify compounds in ginseng that possess anticancer activity. The use of some of these compounds is widely accepted and they are available worldwide. Four countries, Korea, Canada, China, and the USA, are the biggest producers and the total production is ~79,769 tons, and the global ginseng market including roots and other processed parts is estimated to be $2,084 [27]. Our goal is to develop a suitable alternative medicine that has antioxidant as well as anticancer properties; therefore, this review specifically emphasizes the ginseng-derived components, ginsenosides, with anticancer activity, and recent advances in the use of ginsenosides in cancer treatment.

2. Anticancer activities of ginsenosides

Inflammation can derive from both virulent and nonvirulent processes of chronic injury or irritation. The response leads to recruitment of mast cells and leukocytes, with consequent release of free radicals including reactive oxygen species (ROS) that damage macromolecules including DNA and lipids [28]. Cellular and genomic damage occurs as a part of free radical activity and other byproducts. The release of signaling molecules like eicosanoids triggers cell proliferation, which expedites carcinogenesis [28,29]. Inflammation is considered a well-established cancer risk factor that leads to genetic and epigenetic damage, as well as unnatural activation of oncogenes, which causes cancer progression and malignant phenotypes of remodeling, angiogenesis, metastasis, and suppression of innate immune responses [21,30,31]. Therefore, extensive efforts have been made to develop anticancer drugs that show potential effects *in vitro* as well as *in vivo*. With regard to this effort, a number of natural compounds extracted from plants, such as ginsenosides, which are excellent candidates because of their low toxicity and antiangiogenic nature. Ginseng extracts have been reported to possess gastroprotective activity [32], suppress allergic inflammation factors such as interleukin (IL)-4 and IL-5 [33], and suppresses expression of tumor necrosis factor-α and IL-8 in HaCaT cells under LPS treatment [34]. Saponins isolated from Korean Red Ginseng have been reported to suppress NO production, mRNA levels of inducible NO synthase, interferon-β, and COX-2, and block the transcriptional activation of cAMP response element binding protein, activating transcription factor 2, and interferon regulatory factor 3 in LPS-treated macrophages [35]. Research on *in vivo* anticancer studies

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