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·Review·

Red ginseng and cancer treatment

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[ABSTRACT] The ginseng family, including *Panax ginseng* (Asian ginseng), *Panax quinquefolius* (American ginseng), and *Panax notoginseng* (notoginseng), is commonly used herbal medicine. White ginseng is prepared by air-drying after harvest, while red ginseng is prepared by a steaming or heating process. The anticancer activity of red ginseng is significantly increased, due to the production of active anticancer ginsenosides during the steaming treatment, compared with that of white ginseng. Thus far, anticancer studies have been mostly focused on Asian ginseng. In this article, we review the research progress made in the anticancer activities of red Asian ginseng, red American ginseng and red notoginseng. The major anticancer mechanisms of red ginseng compounds include cell cycle arrest, induction of apoptosis/paraptosis, and inhibition of angiogenesis. The structure-function relationship analysis has revealed that the protopanaxadiol group ginsenosides have more potent effects than the protopanaxatriol group. Sugar molecules in ginsenosides inversely impact the antiproliferative potential of these compounds. In addition, ginsenoside stereoselectivity and double bond position also influence the anticancer activity. Future studies should focus on characterizing active red ginseng derivatives as potential anticancer drugs.

[KEY WORDS] Red ginseng; *Panax ginseng*; *Panax quinquefolius*; *Panax notoginseng*; Cancer chemoprevention

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Introduction

Cancer is the second leading cause of death for both men and women in the United States [1]. The clinical management of cancer invariably involves diverse conventional modalities, including surgery, radiation, and chemotherapy [2]. However, the complex characteristics of human cancers require some alternative management to improve the therapeutic efficacy of conventional treatment and the quality of life of cancer patients [3]. Complementary and alternative medicine (CAM) has recently gained closer attention for cancer management. CAM covers a wide spectrum of ancient to new-age approaches that purport to expand options for preventing and treating diseases, including cancer [4]. However, recent surveys indicating a high prevalence of CAM use among cancer patients also reveal low rates of disclosure to physicians, contributing to the growing concerns about CAM among oncologists [5]. While the treatment outcomes of some CAMs are uncertain, attempts have been made to conduct controlled clinical studies of CAM approaches to cancer prevention, treatment, and palliation [5]. Therefore, CAM research offers both exciting opportunities and major challenges.

To evaluate whether CAM has become an integral part of American health care, two comprehensive surveys were conducted by the National Institutes of Health in 2002 and 2007. In the 2002 survey, of 31 044 adults interviewed, 36.0% had used some forms of CAM in past 12 months [6]. In the

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2007 survey, of 23 393 adults interviewed, 38.3% had used CAM in the past year [7]. The most commonly used CAM were natural products (17.7%), deep breathing exercises (12.7%), meditation (9.4%), chiropractic or osteopathic manipulation (8.6%), massage (8.3%), and yoga (6.1%). Thus, natural products, including herbal medicines, are the most commonly used CAM modality in the United States [7].

Herbal medicines have been the major source of therapy in many traditional medical systems and have been used clinically for the treatment of a variety of diseases [8]. Among these herbs, ginseng has a long history and is one of the world's most widely used medicinal plants today [9]. *Panax* L. is a small genus of the family Araliaceae. Nearly all species in the genus *Panax*, such as *Panax ginseng* C. A. Meyer (Asian ginseng), *Panax quinquefolius* L. (American ginseng), and *Panax notoginseng* (Burk.) F. H. Chen (notoginseng), are important herbs used to treat different medical conditions [10-11]. Asian ginseng and notoginseng are considered Chinese herbal medicines, and American ginseng is one of the most commonly used botanicals in North America.

Asian ginseng is commercially available as white and red ginseng in China, Korea, and Japan. White ginseng is prepared by air-drying after harvest. If fresh ginseng is processed by steaming, its color changes to red, and thus the product is called red ginseng [12]. Asian ginseng has been extensively studied and used in the clinic and in general population. Several epidemiological studies have suggested that Asian ginseng can prevent or treat many types of human malignancies [13]. In contrast, anticancer studies of American ginseng and notoginseng are limited and the results are mostly experimentally based. Published studies suggest that red ginseng has more potent anticancer activities than white ginseng [14-15].

In this review, research progresses made in cancer prevention and therapy of red ginseng are summarized. In addition to red Asian ginseng, anticancer related studies on recently developed red American ginseng and red notoginseng are also discussed. Because of the obvious chemical degradation and conversion of original ginsenosides to new compounds during the steaming process, the chemical composition of steamed ginseng is quite different from that of untreated ginseng. The anticancer-related mechanisms of red ginseng compounds, and structure-functional relationship of ginsenoside derivatives are also discussed, which may facilitate the development of these compounds as effective anticancer agents in the future.

Commonly used ginseng herbs

Asian ginseng (Panax ginseng C. A. Meyer)

Asian ginseng is a highly valued herb distributed in Northeastern China, Korea, Far Eastern Russia and has gained popularity in the West. The name ginseng is derived from a Chinese term referring to the "man-like" shape of the root. The genus *Panax*, means "cure all" in Greek. Traditionally, the ginseng root, available in white or red, is used. White ginseng is prepared by air-drying, and red ginseng is prepared by a steaming or heating process [12]. The leaf, berry and other parts of ginseng are also medicinal sources.

Asian ginseng contains different constituents, including ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids [16]. Most of the pharmacological actions of ginseng can be attributed to ginsenosides [10, 17]. Many ginsenosides have been isolated, and novel structures continue to be reported [10].

Ginseng root has been used for centuries in Oriental medicine as a panacea that promotes longevity. The efficacy of ginseng was discovered in the West by the 18th century, and the study of ginseng has a long history. Many studies supported the beneficial effects of Asian ginseng. Recently there has been a renewed interest in investigating ginseng pharmacology using biochemical and molecular biological techniques. Pharmacological effects of ginseng have been demonstrated in the CNS and in cardiovascular, endocrine, and immune systems [16, 18-19]. In addition, ginseng and its constituents have been ascribed antineoplastic, antistress, and antioxidant activities [20-22].

Asian ginseng and its chemical constituents have been tested for their inhibitory effect on human cancers. Several investigators found anticancer properties of ginseng, with ginsenosides Rg3 and Rh2 as the active anticancer saponins [14]. Ginseng extracts were also found to inhibit the growth of breast cancer cells [23]. Our group has investigated the effects of botanical extracts on reducing chemotherapeutic side effects and found that ginseng can attenuate cisplatin-induced nausea and vomiting [24-25]. Additionally, the ginseng extract enhanced the antiproliferation effect of 5-fluorouracil (5-FU) on human colorectal cancer cells, suggesting that it possesses its own anticancer activity [26-27].

American ginseng (Panax quinquefolius L.)

American ginseng is distributed in the eastern temperate forest areas of North America from southern Quebec to Minnesota in the north to Oklahoma, the Ozark Plateau and Georgia in the south. The part of the plant commonly used in remedies is the root. It was first introduced in the *New Compilation of Materia Medica* (*Ben Cao Cong Xin*) by WU Yi-Luo in 1757. In the western world, it was recorded in Quebec, Canada, by Father Lafitau in the early 18th century, and since then has generated a lot of interest [28].

It is believed that the bioactive constituents of American ginseng extract are ginsenosides, which are present in different parts of the plant [10]. A couple dozen of ginsenosides, such as Rb1, Rb2, Rc, Rd, Re, Rg1, and Rg3, have been identified in American ginseng roots [29-30]. Ginsenosides are also distributed in other parts of the herb, including the leaves, flowers and berries [10, 31].

American ginseng is reported to have a wide range of therapeutic and pharmacological applications, such as tonic, antiaging, immunomodulating, anti-fatigue, antidepressant,