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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,

antidiabetic and antitumor activities [16, 32]. Several previous studies of American ginseng focused on the effects on the cardiovascular system, such as anti-ischemic, antiarrhythmic and antihypertensive effects [28, 33]. These pharmacologic effects are, to a significant extent, considered to be linked to the antioxidant properties of the herb. Because there is no typical antioxidant structure in ginsenosides, it was suggested that ginsenosides scavenge free radicals with a protection mechanism for the antioxidant-related protein or enzymes [34].

The effects of American ginseng on cancer treatment and side-effect management were evaluated. These observations include *in vitro* and *in vivo* anticancer activity alone and in combination with chemotherapy [35], potential mechanisms of action of the anticancer effect, chemopreventive effect supported by epidemiologic data, and effects on preventing or alleviating chemotherapy-induced side effects [25].

Notoginseng (Panax notoginseng (Burk.) F. H. Chen)

Notoginseng is a Chinese herbal medicine that has a long history of use in China and other Asian countries. This herb is distributed in Southwestern China, Burma, and Nepal. Notoginseng is cultivated commercially in the southwestern regions of China, especially in Yunnan Province. The portion of the plant commonly used in remedies is the root, which is dug up after the fruit has ripened [36].

The earliest scientific description of notoginseng was in *Materia Medica* (*Ben Cao Gang Mu*), a dictionary of Chinese herbs, written by LI Shi-Zhen (1518−1593 AD). In *Materia Medica*, notoginseng was called “more valuable than gold”, indicating the significance of this herb in traditional Chinese medicine [37].

The main bioactive compounds in notoginseng are dammarane saponins, commonly referred to as ginsenosides and notoginsenosides. Oleanane-type saponin, present in Asian ginseng and American ginseng, is not found in notoginseng. Over 60 saponins have been isolated from the notoginseng plant. Most of them belong to the protopanaxadiol group, while others belong to the protopanaxatriol group [37-38]. Ginsenosides Rb1, Rg1, and Rd and notoginsenoside R1 are the main saponins in the notoginseng roots [39].

Notoginseng is regarded as the emperor herb in the treatment of different types of wounds because it is a favorite medicine for both internal and external hemorrhage [40]. Notoginseng can also decrease blood pressure, improve blood supply and protect against shock, and protect the cardiovascular system and brain vasculature [36, 41]. Its protective mechanism is partly due to protection against damage by oxygen free radicals, and also by binding to the estrogen receptor, as ginsenosides share many of the protective actions of estrogen in various physiological systems [42-43]. Notoginseng extracts were also found to possess the capacity to adjust energy metabolism and treat diabetes [44].

Some studies also showed that notoginseng has antitumor effects [45-47]. Recently, our group found that notoginseng extract can increase the effects of 5-FU, a commonly used cancer chemotherapeutic agent. Since it is well known that 5-FU has cytotoxic effects on primary cells, the synergistic effect between notoginseng and 5-FU makes it possible to reduce the dose of 5-FU in combination with notoginseng extract and thereby further decrease dose-related toxicity [48].

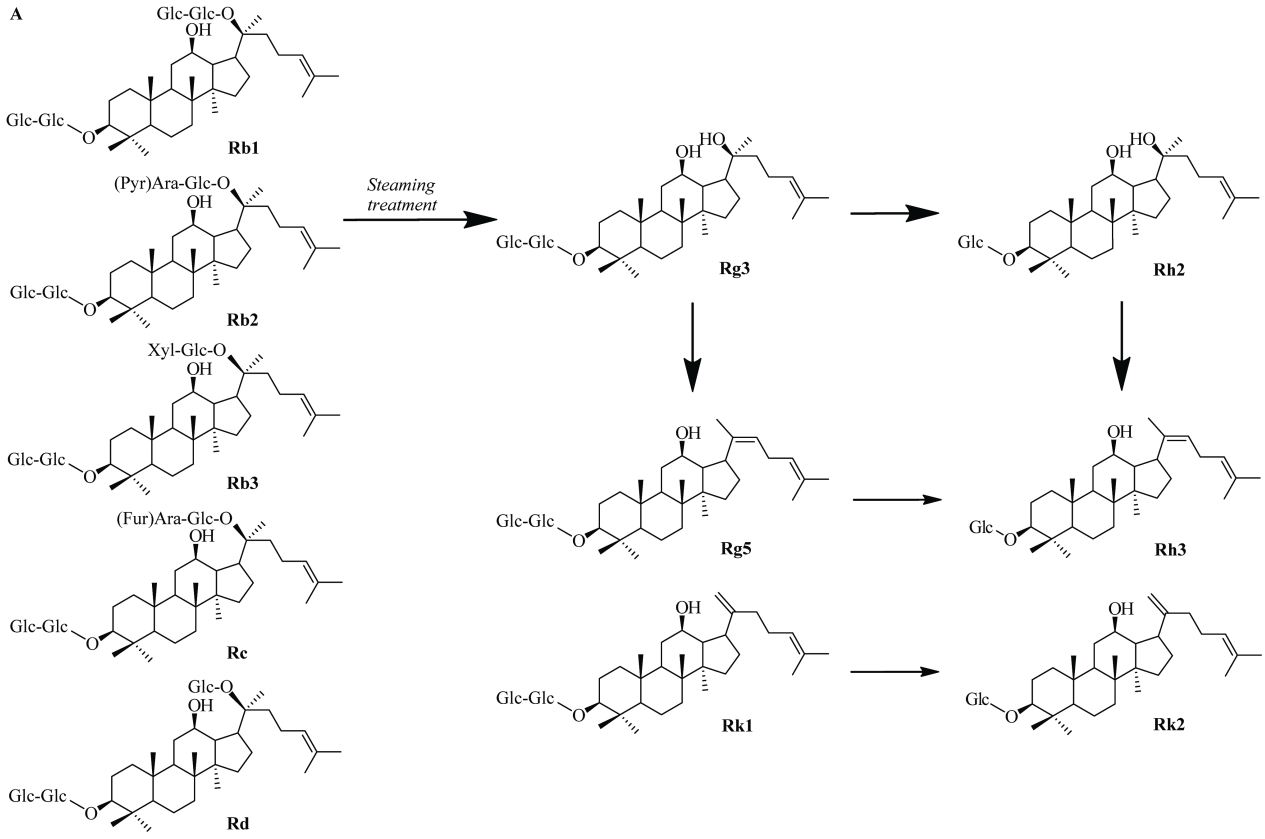
Steam processing changes ginsenoside structures

In Asia, ginseng root is air-dried into white ginseng or steamed at 100 ℃ for several hours to produce red ginseng [49-50]. It is believed that red ginseng is more pharmacologically effective than white ginseng. The differences in the biological effects of white and red ginseng are attributed to the significant changes in ginsenosides from the steaming treatment. Compared with white Asian ginseng, red ginseng has stronger anticancer activities [14], due to a relatively high content of the ginsenoside Rg3. It seems likely that the steaming process or heat-treatment of ginseng is a good approach to transfer inactive ginsenosides to active anticancer compounds such as ginsenoside Rg3, Rh1, Rh2, and their aglycones [49].

The optimum steaming condition for American ginseng is at 120 ℃ for 4 h [51]. Because of obvious chemical degradation and conversion of the original saponins to new compounds during the steaming process, the chemical composition of steamed American ginseng is quite different from that of the untreated ginseng. After steaming, the original polar ginsenosides decrease considerably and the less polar ginsenosides increase [51-52]. The less polar compounds are not detected or are present in small amounts in untreated ginseng.

Constituent changes of notoginseng after steaming treatment have also been reported. After steaming treatment, the content of major ginsenosides Rb1, Rg1, Rd and notoginsenoside R1 decreased, while that of less polar ginsenosides increased. The major markers in red notoginseng include three groups of epimers or geometric isomers, namely 20(*S*)-Rg3 and 20(*R*)-Rg3, Rk3 and Rh4, Rk1, and Rg5 (Fig. 1). These compounds are not detected or are only present in trace amounts in unsteamed notoginseng [15, 39]; this trend is very similar to what occurs after the steaming of Asian ginseng and American ginseng.

In three ginseng plants, representative ginsenosides are classified as protopanaxadiol (PPD) and protopanaxatriol (PPT) groups. For ginsenosides in the PPD group, e.g. ginsenosides Rb1, Rb2, Rb3, Rc, and Rd, it is easy to selectively eliminate the carbon-20 sugar chain to produce 20(*S*)/(*R*) Rg3. The generated content of 20(*S*)-Rg3, however, is higher than that of 20(*R*)-Rg3. Due to the presence of the chiral carbon in carbon-20, there are several groups of 20(*S*) and 20(*R*) epimers in white and red ginsengs like 20(*S*)/20(*R*)-Rg2, 20(*S*)/20(*R*)-Rg3, and 20(*S*)/20(*R*)-Rh2 [10]. In particular, 20(*S*) and 20(*R*) are epimers of each other, depending on the position of the hydroxyl (OH) group on carbon-20. This epimerization is known to be produced by the selective attack of the OH



B

Number of sugar molecules	Parent ginsenosides in untreatd ginseng		Ginsenoside derivatives in red ginseng	
	4-sugar ginsenosides	3-sugar ginsenoside	2-sugar derivatives	1-sugar derivatives
Ginsenosides	Rb1, Rb2, Rb3, Rc	Rd	Rg3, Rg5, Rk1	Rh2, Rh3, Rk2
Hydrophilicity	+++	++	+	+/–
Anticancer potential	–	+/–	++	+++

Fig. 1 Effects of steaming treatment on protopanaxadiol group ginseng saponin conversion and anticancer activity. (A) Ginsenoside structural changes during steaming treatment. Abbreviations for sugar residues: Glc, *β*-D-glucose; Ara(Pyr), *α*-L-arabinose(pyranose); Ara(Fur), *α*-L-arabinose(furanose); and Xyl, *β*-D-xylose. (B) Ginsenoside derivatives have different anticancer activities. Sugar molecule numbers have an inverse impact on anticancer potential

group after the elimination of the glycosyl residue at carbon-20 during the steaming process [53]. Rg3 could be further transformed to two geometric isomers, namely Rk1 and Rg5, by dehydration. The formed Rk1 and Rg5 represent positional isomers of the double bond at carbon-20(21) or carbon-20(22) (Fig. 1). It was found that the epimers and geometric isomers presented similar retention times under most liquid chromatographic conditions. 20(*S*) ginsenoside was usually eluted earlier than its relevant 20(*R*) epimer, and 20(21)-geometric isomers were eluted earlier than their relevant 20(22)-isomers [54]. Only a low abundance of Rh2 was observed in red ginseng, implying the elimination of carbon-3 sugar residue is relatively difficult in the steaming process.

On the other hand, the PPT group ginsenosides (R1, Rg1, Rf, and Re) tend to lose (20)glc residue firstly and subsequently its terminal sugar unit at carbon-6 to form 20(*S*)/20(*R*)-Rg2 and/or Rh1. Rh1 is further converted to Rk3 and Rh4 by dehydration at carbon-20. The above results suggested that the elimination of sugar chains at carbon-20, then at carbon-6 or at carbon-3, and then the subsequent dehydration reaction at carbon-20 are commonly observed in the steaming process [55]. The carbon-20 sugar moiety is the most thermally unstable, followed by carbon-6 and then carbon-3 sugar moieties.

Other than saponins, ginseng also contains other constituents, including flavonoids, polyacetylenes, phytosterols, essencial oils, acids, polysaccharides, nitrogen-containing compounds and vitamins. During the steaming process, the structures of these compounds could also be altered. However, previous studies often only focused on ginseng saponins. The structural changes of other compounds and subsequent changes in their biological activities remain largely unknown, which need to be

evaluated in the future studies.

Anticancer activities of steamed ginseng

Ginseng has many reported health benefits [16]. Regarding its anticancer effects, a case-control study on over a thousand Korean subjects shows that long-term ginseng consumptionis associated with a decreased risk for many different cancers, compared with those who do not consume ginseng [56-57]. It also suggested that ginseng has a non-organ specific preventive effect against cancers [13]. It has been reported that the anti-carcinogenic effects of white ginseng are more prominent after being heat-treated or steamed [58]. The enhanced anti-carcinogenic effects of red ginseng are linked to the inhibition of lipid peroxidation and regulation of the targets involved in the cytochrome P450 signaling pathway [59].

Steam-processing can yield very high amount of active ginsenosides. More specifically, our group has performed a systematic comparison of the ginsenosides and anticancer activities among the white (air-dried) and red (steamed) roots of Asian ginseng, American ginseng, and notoginseng, and observed that, due to the conversion of the original polar ginsenosides in white ginseng to novel, less polar, degradation compounds in red ginseng, white ginseng produces weak antiproliferative effects, while red ginsengs exhibits a significant increase in antiproliferative and pro-apoptotic effects, with red notoginseng exhibiting the greatest anticancer activities [15, 51-52, 60]. The next logical step in the study of red ginseng anticancer activity should be to systemically compare the differences in chemical composition among three red ginsengs and reveal the linkage between ginsenoside derivatives and their related anticancer activities.

The main active components of red ginseng for cancer prevention are believed to be ginsenosides Rg3, Rh2, Rg5, and PPD, and these compounds work singularly and/or synergistically [58, 61]. Among these ginsenosides, Rg3 and Rg5 show significant reductions in lung tumor incidence when examined in a medium-term lung carcinogenesis mouse model [58]. Additionally, red ginseng works singularly as well as synergistically with chemotherapeutic agent 5-FU to exert antiproliferative effects on a human colorectal cancer cell model [26]. Epirubicin and paclitaxel are two important chemotherapeutic agents widely used to treat a broad spectrum of cancers. Because of their significant adverse effects, developing adjuvant agents to reduce their adverse effects are urgently needed. Red ginseng significantly potentiated the anticancer activities of epirubicin and paclitaxel in a synergistic manner; thus, their dose and the dose-related adverse events could be reduced. Red ginseng treatment activated caspases 3 and 9, increased the mitochondrial accumulation of both Bax and Bak that led to an enhanced cytochrome c release, and induce apoptosis [62]. In another recent study, the protective mechanism of red ginseng in anticancer drug-induced toxicity was observed through the regulation of NF-κB activities [63].

Along with its anti-carcinogenic and antitumor activities, red ginseng also has anti-inflammatory and antioxidant activities, which also contribute to its chemopreventive effects. Recently, the important link between inflammation and carcinogenesis has begun to be elucidated, and it is thought that red ginseng may exert some of its cancer chemopreventive effects by stopping inflammatory carcinogenesis [64]. There are several key molecular players that link inflammation to carcinogenesis, including prostaglandins, cytokins, chemokines, angiogenic growth factors, and free radicals. These factors, coupled with other risks and processes, lead to increased mutations and altered functions of important enzymes and proteins, which contribute to the carcinogenic process. Red ginseng is thought to attenuate inflammation-associated carcinogenesis through a variety of pathways by scavenging reactive oxygen species, reducing Cox-2, iNOS, and NF-κB, inhibiting proliferation, and inducing a dual anti-angiogenic effect on carcinogenesis [64]. In summary, red ginseng exerts its anticancer effects through a variety of pathways and can be used alone or in combination with other chemotherapeutic agents.

Red ginseng compounds and anticancer mechanisms

In recent years, as techniques have been developed for chemical purification and structural identification, novel ginseng saponins continue to be characterized. In steamed red ginsengs, ginsenosides Rg3, Rh2, Rg5, Rk1, Rk3, and Rh4 and aglycones PPD and PPT have shown stronger anticancer potential than their parent compounds in untreated white ginseng [55]. Their anticancer potentials were observed by *in vitro* cell antiproliferative determinations and verified by *in vivo* antitumor evaluations. Anticancer related mechanisms were found to be linked with cell cycle arrest, induction of apoptosis and paraptosis, and inhibition of angiogenesis.

Cancer cells lack normal growth controls, exhibit loss of cell cycle control, and have unlimited reproductive potential and growth-signal self-sufficiency. Any compounds aimed at controlling these processes would be beneficial in suppressing the progression of cancers [65]. Several ginsenosides including Rg3, Rh2, and PPD have been shown to block the cell cycle progression. G1 phase or G1/S boundary appears to be arrested via different mechanisms [66-67]. Rh2 blocks the cell cycle at the G1/S boundary by selectively inducing the expression of p27Kip1 [68]. Rg5 and Rs4 (acetylated Rg5) achieve similar effects by selectively elevating the levels of p53 and p21WAF1 [69]. Recently, our group observed that PPD arrested cancer cell cycle at G1 phase, which is mediated by targeting NF-κB, JNK, and MAPK/ERK signaling pathways [70].

Apoptosis is programmed cell death involving the activation of caspases through either a mitochondria-dependent cell intrinsic or mitochondria-independent cell extrinsic pathway. Currently, many researches are focused on

exploring novel compounds that can regulate cell proliferation and apoptosis in order to elucidate new candidates for cancer therapy [71]. Red ginseng and active ginsenosides target signaling intermediates in apoptotic pathways. It was found that red ginseng compounds Rg3, Rh2 and PPD alter the mitochondrial membrane permeability, promote the release of cytochrome c into the cytosol, activate caspase proteases, and cleave poly ADP ribose polymerase [72-73]. The activity of cyclin-dependent kinases also may be associated with the depolarization of mitochondrial membrane potential during ginsenoside-induced apoptosis. In the death receptor-mediated pathway, ginsenosides increase the expression of the DR4 death receptor and activate caspases 8 and 3 [74]. By regulating the interactions between p53 and DR4/DR5, our group observed that the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) pathway is associated with PPD's cancer chemotherapy [75].

In addition to apoptosis, several types of caspase independent programmed cell death have been identified, including paraptosis, which is characterized by cytoplasmic vacuolization, lacks apoptotic morphology, and does not respond to caspase inhibitors [76]. Recently, our group observed that ginsenoside Rh2 and PPD induced cell death is partially dependent on caspase 3 activation. Interestingly, we also found that Rh2 and PPD induce a significant level of cytoplasmic vacuole formation, which is characteristic of paraptosis. Rh2 and PPD treatment activated the NF-κB pathway to protect the cancer cells from cell death while simultaneously activating two different cell death pathways. In addition, Rh2 and PPD activated the p53 pathway, which contributed to the induction of both apoptosis and paraptosis-like cell death [77-78].

Angiogenesis is the process by which new blood vessels are formed from pre-existing structures. Since the uncontrolled growth of solid tumors is closely related to tumor angiogenesis by delivering nutrients and oxygen for the survival of tumor cells, adequate control of tumor angiogenesis has been an attractive target for tumor therapy [79]. Red ginseng inhibits tumor growth by influencing neovascularization and the angiogenesis-related properties of endothelial cells. Endothelial cell markers, such as CD-31, are often used to measure angiogenesis [80]. Ginsenoside Rg3 inhibits proliferation, formation of capillary tube, and chemoinvasion of endothelial cells induced by vascular endothelial growth factor [81]. The angiosuppressive effect of Rg3 may be related to the differential regulation of matrix metalloproteinase (MMP)-2 and -9 activities [81]. Rg3 effectively abrogated the vascular endothelial growth factor (VEGF) dependent on neovessel formation and attenuated endothelial progenitor cell mobilization, leading to delayed tumor progression and tumor angiogenesis [82].

Other pathways such as those that prevent the metastatic spread of cancer or reduce inflammatory responses are also reported to be part of the chemopreventive and therapeutic effects of red ginseng compounds [83-84].

Structure-activity relationship of ginsenosides

Ginseng saponins belong to a family of triterpene glycosides or triterpene saponins. Ginseng saponins (except ginsenoside Ro) possess the four trans-ring rigid steroid skeleton, with a modified side chain at carbon-20. Sugar residues are attached to the -OH of the aglycone. Ginseng saponins can mainly be classified as protopanaxadiol group and protopanaxatriol group [10].

For the protopanaxadiol group, sugar residues are attached to the β-OH at carbon-3 and another -OH at carbon-20 of the aglycone, such as ginsenoside Rb1, Rc, Rd, Rg3 and Rh2. For the protopanaxatriol group, sugar residues are attached to the α-OH at C-6 and another -OH at carbon-20 of the aglycone, such as ginsenoside Re, Rg1, Rg2, Rh1 and notoginsenoside R1 [10, 36].

Structure-activity relationship elucidates the relations between chemical structure and their pharmacological activity for a series of compounds. The anticancer activities of ginseng saponins are correlated with the type of aglycones and sugar residues. Sugar molecules within a ginsenoside have a high impact on tumor cells. Anticancer activities increase with the decrease of sugar number (Fig. 1). Ginsenosides with three or more sugar molecules (*e.g.*, Rb1, Rb2, Rb3, Rc, and Rd) show no or very weak antiproliferative effects [29, 55]. Ginsenosides Rg3, Rg5 and Rk1 (two sugars), Rh1, Rh2, Rh3, Rh4, Rk2, and Rk3 (one sugar), PPD and PPT (no sugar) inhibit different types of cancer cells [55]. Interesting, during the steaming process, the length of sugar moiety in ginsenoside was reduced, thus increasing its anticancer activities.

Differences in sugar linkage positions may influence biological responses. In a comparasion of sugar moiety connected with the postions of carbon-3 or carbon-6, the carbon-6 substituent differentiates the two groups of ginsenosides structurally. Ginsenoside Rh2 (PPD type) and Rh1 (PPT type), which possess a glucose linkage at carbon-3 and carbon-6 respectively, have similar chemical structures, but the anticancer effect of Rh2 is stronger than that of Rh1 [85]. With a sugar substitute at carbon-6, the anticancer activity of ginsenosides is attenuated compared to the activity with linkages at carbon-3 or carbon-20. Molecular modeling and docking confirm that any sugar moiety at carbon-6 increases the steric hindrance of these molecules to target proteins [86]. Steric hindrance blocks entrance into the extracellular binding pocket for binding to their targets, thus significantly reducing the anticancer activities of ginsenosides. Overall, the protopanaxadiol group ginsenosides have more potent effects than those of the protopanaxatriol group. The anticancer potency of ginsenosides was found to be in the order: carbon-3 > carbon-6 > carbon-20 [55].

20(*S*) and 20(*R*) are stereoisomers of each other that

depend on the position of the carbon-20 hydroxyl in ginsenosides. 20(*S*)-OH is geometrically close to the carbon-12 hydroxyl of ginsenosides. 20(*R*)-OH is far from the carbon-12 hydroxyl. The different stereochemistries of the 20(*R*)- and 20(*S*)-ginsenosides produce different pharmacological effects. Although 20(*S*) and 20(*R*)-Rg3 show similar activity, for the pair of PPD ginsenosides, 20(*S*)-Rg3 has more significant potent antiproliferative effects than 20(*R*)-Rg3, suggesting that 20(*S*)-ginsenosides have stronger anticancer potential than their 20(*R*)-stereoisomer [87-88].

In addition, the position of the double bond also influences anticancer activities. In red ginseng, rare ginsenosides with a dehydroxylated structure are identified during the steaming process. Ginsenosides Rk3/Rh4, Rk1/Rg5 and Rk2/Rh3 are the dehydroxylated products of Rh1, Rg3, and Rh2 at carbon-20, respectively. A recent report has indicated that ginsenosides Rk1 and Rk3 with the double bond at C20-21 show higher anticancer effects than Rg5 and Rh4 with a double bond at C20-22 [55]. Thus, ginsenosides with a double bond at C20-21 exhibit more effective anticancer activities than those at C20-22.

Conclusions

Ginsengs, including Asian ginseng, American ginseng and notoginseng, are some of the most commonly used herbal medicines. The investigations of the effects of ginsengs in cancer chemoprevention and therapeutics have attracted researchers' attention in past several decades. Compared to unsteamed white ginseng, the anticancer activities of red ginseng are significantly increased due to major ginsenosides with low anticancer activity such as Rb1, Rg1 and Re being converted to active anticancer ginsenosides such as Rg3, Rk1, Rh1, and Rh2. Ginsengs are saponin-rich botanicals and steam-processing can yield a very high amount of active ginsenosides. Based on the above discussion, the emphasis of future studies should be placed on characterizing active red ginseng compounds in relation to its anticancer actions. In addition, it is worthy further exploring the systemic differences in chemical compositions among the three red ginsengs and the linkage between ginsenoside derivatives and their antitumor potential. Since ginseng also contains other compounds in addition to saponins, how the structural changes of other ginseng compounds influence their anticancer effects needs to be further characterized. Nevertheless, the revealed structure-activity relationship provides important information for further semi-synthesis of ginsenoside derivatives for discovery of novel anticancer drugs.

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