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Commentary

American ginseng: Potential structure–function relationship in cancer chemoprevention

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ABSTRACT

Ginseng has a prominent position on the list of best-selling herbal products in the world, and its main active constituents are thought to be ginsenosides. Compared with the long history of use and widespread research on Asian ginseng, studies of American ginseng are relatively limited, especially regarding cancer chemoprevention. In recent studies of American ginseng, steaming or heating altered the ginsenoside profile and thereby increased anticancer effects. Yet the ginsenoside structures and their activities have not been systematically elucidated. In this commentary, we introduce the different ginsenosides in American ginseng, both the naturally occurring compounds and those resulting from steaming or biotransformation. We briefly review American ginseng's reported anticancer effects and their mechanisms of action, and explore the possible structural-function relationship with a focus on sugar molecules, hydroxyl groups and stereoselectivity in ginsenosides. Understanding these relationships may produce insights into chemical and pharmacological approaches for enhancing the chemopreventive effects of ginsenoside and for developing novel anticancer agents.

1. Introduction

As a medicinal herb, ginseng has been used for thousands of years in the Far East, and in the last two decades has gained great popularity in the West [1–3]. There are two major species of ginseng, i.e., *Panax ginseng* or Asian ginseng and *Panax quinquefolius* L. or American ginseng [3,4]. Compared with the long history of use and widespread research on Asian ginseng [3,5,6], studies of American ginseng and its constituents are limited [7], in spite of some promising advances in recent years [8,9]. The pharmacological effects of American ginseng have been observed in the central nervous, cardiovascular, endocrine, and immune systems [1,7,8]. Another reported action of American ginseng is cancer chemoprevention and inhibition of tumor growth [2,9,10].

The constituents isolated and characterized in American ginseng include ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids [1,4]. The main active ingredients are thought to be the ginsenosides [11,12]. Recent studies have shown that steaming or heating American ginseng alters its ginsenoside profile and increases anticancer activities [13,14]. The metabolic processing of ginsenosides can also change the therapeutic effects of ginseng [15,16]. To date the correlation of various ginsenosides to anticancer activities is still not well elucidated. Insufficient information about the structure–activity relationship of ginsenosides has delayed the progress of drug development with ginsenosides.

In this commentary, we introduce the ginsenosides in American ginseng, both the naturally occurring compounds and those resulting after steaming or biotransformation. We briefly review American ginseng's reported anticancer effects and their mechanisms of action, and explore the possible structural-function relationship with a focus on sugar molecules, hydroxyl groups and stereoselectivity in ginsenosides. An understanding of this relationship is a prerequisite for purposeful modifications to produce novel agents for use in medical oncology.

2. Ginsenosides isolated from American ginseng

2.1. Structural diversity of ginsenosides

Ginsenosides belong to a family of steroids named steroidal saponins [1,11]. They also have been called ginseng saponins,

Abbreviations: COX-2, cyclooxygenase-2; ECs, endothelial cells; IC_{50}, 50% inhibitory concentration; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; Pgp, P-glycoprotein; PPD, protopanaxadiol; PPT, protopanaxatriol.

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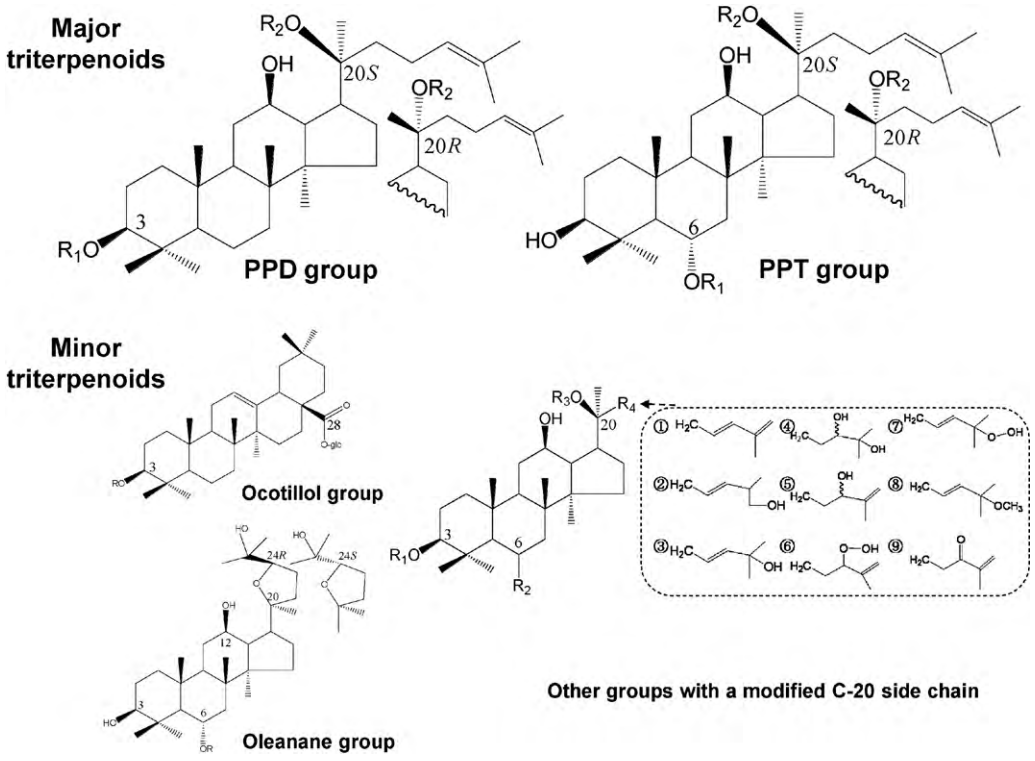

Fig. 1. Core structures of different types of triterpenoid saponins from American ginseng. The major saponins include the protopanaxadiol (PPD) group and the protopanaxatriol (PPT) group. The minor saponins include the ocotillol group, the oleanane group and other groups with a modified C-20 side chain. The groups with the modified C-20 side chain can be further subdivided: ①, e.g. quinquenoside-L1; ②, e.g. quinquefoloside-L2; ③, e.g. quinquenoside-L3; ④, e.g. quinquefoloside-L9; ⑤, e.g. majoroside-F1; ⑥, e.g. notoginsenoside-C; ⑦, e.g. notoginsenoside-K; ⑧, e.g. quinquefoloside -La; and ⑨, e.g. ginsenoside III.

triterpenoid saponins, or dammarane derivatives [4,12]. More than 60 ginsenosides have been isolated from the roots, leaves, stems, flower buds and berries of American ginseng [4,17–20], and novel structures continue to be discovered [18,21]. Most ginsenosides share a dammarane triterpenoid structure with a four trans-ring rigid steroid skeleton [1,17]. Ginsenosides differ from one another by sugar type, number, and linkage position [4,12]. The stereoisomerism and a changeable side chain at C-20 also contribute to the structural diversity of ginsenosides [17,18].

As illustrated in Fig. 1, ginsenosides from American ginseng can be divided into several groups. The protopanaxadiol (PPD) group has sugar moieties attached to the β-OH at C-3 and/or C-20 [4]; the protopanaxatriol (PPT) group has sugar moieties attached to the α-OH at C-6 and/or β-OH at C-20 [17]; the ocotillol group has a five-membered epoxy ring at C-20 [18]; the oleanane group has a non-steroidal structure [19], and other groups have a modified C-20 side chain [18]. We consider the PPD and PPT groups primarily. The others have a low or trace presence in American ginseng [11,20].

The ginsenoside content of the different parts of American ginseng varies, ranking in decreasing order from leaf to root-hair to rhizome to root to stem [20]. In general, ginsenosides Rb_1, Re, Rd, Rc, Rg1 and Rb3, the six major saponins, make up more than 70% of total ginsenoside content in American ginseng [11,22]. Variability in individual ginsenosides and total ginsenoside content has been observed in different commercial products of American ginseng because of natural variations such as climate and geographical location, cultivation length and conditions [22,23]. Ginsenoside variability in different ginseng products also may be responsible for the contradictory pharmacological activities that have been reported [10]. Consequently, there is a need for standardization and regulation of herbal products such as ginseng.

In the herbal market, American ginseng is sometimes adulterated with Asian ginseng [24,25]. The presence of 24(*R*)-pseudoginsenoside F_{11} in American ginseng and ginsenoside Rf in Asian ginseng distinguishes them from each other [26]. Establishing the ratio of Rg1/Rb1 and Rb2/Rb1 is also useful. Ratios less than 0.4 indicate American ginseng; higher ratios are characteristic of Asian ginseng [12]. One exception is that a high Rg1/Rb1 ratio is found in wild American ginseng [27].

2.2. Structural changes in ginsenosides after steaming treatment

Ginseng is commercially available in white and red [28]. White ginseng is prepared by air-drying after harvest, and red ginseng is prepared by a steaming or heating process [29]. The optimum steaming condition for ginseng is at 120 °C for 4 h [30]. Treated ginseng has more potent activities on human cancer cells than does white ginseng [13,28]. Because of obvious chemical degradation and conversion of original saponins to new compounds during the steaming process, the chemical composition of steamed American ginseng is quite different from untreated ginseng [28,31,32]. As shown in Fig. 2A, after steaming, the original polar ginsenosides Rg_1, Re, Rb_1, Rc, Rb_2, Rb_3, and Rd decrease considerably and the less polar ginsenosides 20(*S*)/20(*R*)-Rg2, 20(*S*)/20(*R*)-Rg3, Rk3, Rh4, Rk1 and Rg5 increase [28,32]. The less polar compounds are not detected or are present in small amounts in untreated ginseng [13].

The structural changes in ginsenosides after a steaming treatment are shown in Fig. 2B. The major changes are elimination of sugar moiety first at C-20, then at C-6 or C-3, and subsequent dehydration at C-20. In the PPD group of ginsenosides (Rb1, Rc, Rb2, Rb3 and Rd), the C-20 sugar chain is eliminated to produce 20(*S*)/20(*R*)-Rg3. Rg3 is further transformed to two geometric isomers namely Rk_1 and Rg5 by dehydration. Rg3 is also changed to 20(*S*)/20(*R*)-Rh2 and PPD by loss of the terminal sugar residue and subsequently one more sugar at C-3. The formed 20(*S*) and 20(*R*)-Rg3 represent a typical stereoisomer by the selective attack of the hydroxyl group after elimination of the glycosyl residue at C-20. Rk1 and Rg5 represent a positional isomer of the double bond at C-

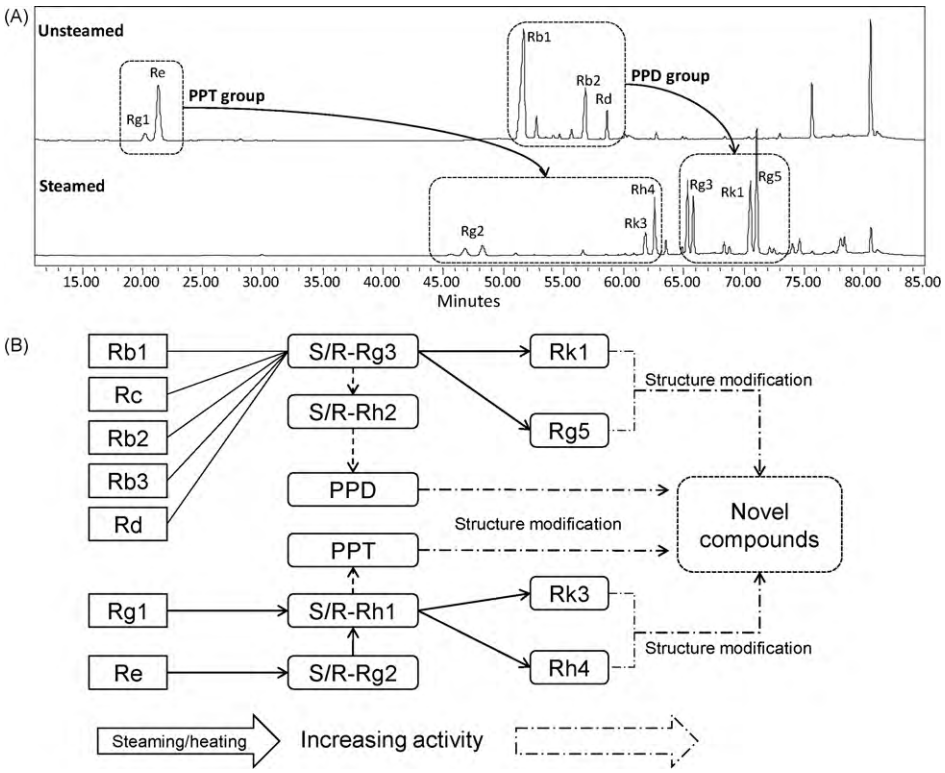

Fig. 2. (A) Typical high-performance liquid chromatography-UV chromatograms of unsteamed and steamed (120 °C for 4 h) American ginseng roots. (B) Major ginsenoside structural changes during the steaming process. "→" denotes major process; "– –>" denotes minor process; "– ·–>" denotes potential chemical modifications for novel compounds. The major structural changes include first elimination of sugar moiety at C-20, then at C-6 or C-3, and subsequent dehydration at C-20 in ginsenosides.

20/21 or C-20/22 [33]. The epimers and geometric isomers appear similar on chromatography, but 20(*S*) is usually eluted earlier than the 20(*R*) epimer, and the 20/21 double bond ginsenoside is eluted earlier than the 20/22-isomer [14]. There is little Rh2 in steamed American ginseng, implying that the C-3 sugar residue is difficult to eliminate in the steaming process [13]. Chemically, Rk1, Rg5, and PPD can be transformed to their degradation products Rk2, Rh3, and 20-dehydration-PPD under more intense conditions or by structure modification. Similar structural changes were observed in PPT group.

In steamed American ginseng, ginsenosides Rg3 [34,35], Rh2 [36,37], Rg5 [38], PPD [39,40] and PPT [41] show stronger anticancer potential than ginsenosides in untreated ginseng. The past several years have witnessed some developments in extraction, purification, structure elucidation and bioassay-guided fractionation of American ginseng [17,18]. After identifying ginsenoside leads like PPD, investigators have been applying synthetic methodologies, biotransformation and combinatorial biosynthesis to modify the lead compounds [17,42]. Chemical modification generates a large number of novel and structurally diverse analogs for potentially improved anticancer activities [4,43].

2.3. Biotransformation of ginsenosides

As a dietary supplement, American ginseng is usually taken orally. Therefore, the metabolism of ginsenosides has attracted attention [44–46]. In contrast to the many reports describing ginseng pharmacology, studies on the herb's pharmacokinetics are somewhat limited. The oral bioavailability of ginsenosides from the gastrointestinal tract is low to 5% or less. [44,45]. The half-life of ginsenosides in humans is generally less than 24 h [45,46]. A small 0.2%-1.2% of ginsenosides can be expected in urine [44].

A commonly expressed concern about ginsenosides is the extensive metabolism in the gut [45,46]. Studies of the degradation and metabolism of ginsenosides have been conducted using enzymes or intestinal bacteria [45–47]. The main metabolic pathways include deglycosylation reactions by intestinal bacteria *via* stepwise cleavage of the sugar moieties [45]. PPD group such as Rb1 and Rd are metabolized to IH-901 (also known as compound K or M1) [15,16] and then changed to the PPD aglycone [47]. Rg3 and Rg5 are biotransformed to Rh2 and Rh3, respectively. PPT group such as Rg1 and Re are mainly converted to Rh1 and F1, and then to the PPT aglycone [45,46]. Consequently, after oral administration, not parent ginsenosides but their metabolites are absorbed from the gut into systemic circulation [44,46].

In vitro and *in vivo* comparisons using intestinal bacterial suggest that ginseng's anticancer activities appear to be affected by the metabolites [15,45]. Parental metabolites are further esterified with fatty acids in liver and tissues, and the resultant fatty acid conjugates are sustained longer in the body [48]. Fatty acid esterification might potentiate the antitumor activity of the metabolites through delay of clearance [45,48].

3. Anticancer activities and possible mechanisms

Tumor malignancy results from a complex interaction between multiple genes, within the cell itself, and with its neighboring tissues [49]. There are some but not systematic reports of the action of American ginseng on its cellular and molecular targets through various signaling pathways [50]. Some of these observations are described below and summarized in Fig. 3.

3.1. Regulation of cell cycle

Many anticancer agents act by blocking one or more stages of the cell cycle [51]. Some genes (e.g., p53) and proteins (e.g., the

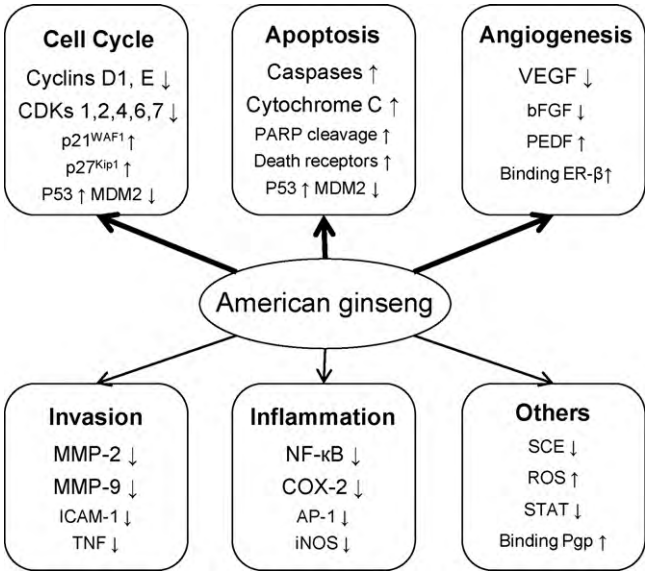

Fig. 3. Possible cellular and molecular mechanisms of American ginseng against cancer. "→" denotes major pathways, "→" denotes additional pathways. CDKs, cyclin-dependent kinases; MDM2, murine double minute-2; PARP, poly ADP ribose polymerase; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; FEDF, pigment epithelium-derived factor, ER-β, estrogen receptor-β; MMP, matrix metalloproteinase; ICAM-1, intercellular adhesion molecule-1; TNF, tumor necrosis factor; NF-κB, nuclear factor κB; COX-2, cyclooxygenase-2; AP-1, activator protein-1; iNOS, inducible nitric oxide synthase; SCE, sister chromatid exchanges; ROS, reactive oxygen species; STAT, Signal transducer and activator of transcription; Pgp, P-glycoprotein.

cyclins and the cyclin-dependent kinases) are known to regulate the timing of the events in the cell cycle. Propidium iodide staining is commonly used to detect cell cycle events [52,53]. Several ginsenosides including Rg3, Rh2, IH-901 and PPD have been shown to block the cell cycle progression. G1 phase or G1/S boundary appears to be arrested *via* different mechanisms [51–54]. For example, Rh2 blocks the cell cycle at the G1/S boundary by selectively inducing the expression of $p27^{Kip1}$ [53]. Rg5 and Rs4 (acetylated Rg5) achieve similar effects by selectively elevating the levels of p53 and $p21^{WAF1}$ [51]. IH-901 arrests the G1 phase by activation of c-Jun N-terminal kinase [54]. Further studies are needed to confirm the mechanisms of cell cycle arrest using related inhibitors or siRNA to knockdown observed genes and proteins.

3.2. Induction of apoptosis

Apoptosis is a selective process of physiological cell deletion to maintain a balance between cell replication and cell death [15]. Steamed American ginseng targets signaling intermediates in apoptotic pathways [55,56]. A number of ginsenosides such as Rh2 [36], PPD [57], PPT [57], and IH-901 [15,16] trigger cancer cell apoptosis [36]. Apoptotic biomarkers such as TUNEL and annexin V assays are used to see early phase as well as late event of apoptosis [55–58].

Ginseng induces apoptosis by two different pathways, the intrinsic mitochondrial-mediated pathway [55], and the extrinsic death receptor-mediated pathway [36]. In the first, ginseng alters the mitochondrial membrane permeability, promotes the release of cytochrome *c* into cytosol, activates caspase-9 and -3 protease, and cleaves poly ADP ribose polymerase [15,55,58]. The activity of cyclin-dependent kinases also may be associated with depolarization of mitochondrial membrane potential during ginsenoside-induced apoptosis [59]. In the death receptor-mediated pathway, ginsenosides increase the expression of the DR4 death receptor and activate the caspase-8 and -3 [16,36].

3.3. Inhibition of angiogenesis

Angiogenesis is the process by which new blood vessels are formed from pre-existing structures [60]. It is a crucial step in tumor growth and metastasis by supplying oxygen and nutrients [60]. American ginseng inhibits tumor growth by influencing neovascularization and the angiogenesis-related properties of endothelial cells (ECs) [61]. Endothelial cell markers such as CD-31 are often used to measure angiogenesis [60,61]. Ginsenoside Rb1 has been shown to inhibit capillary morphogenesis of ECs by regulating pigment epithelium-derived factor through estrogen receptor β [61]. 20(*R*)-Rg3 inhibits proliferation, formation of capillary tube, and chemoinvasion of ECs induced by vascular endothelial growth factor [34]. 20(*R*)-Rg3 also reduces microvascular sprouting *in vitro* and inhibits neovascularization induced by basic fibroblast growth factor *in vivo* [34]. The angiosuppressive effect of 20(*R*)-Rg3 may be related to the differential regulation of matrix metalloproteinase (MMP)-2 and -9 activities [34].

In contrast, Rg1 promotes functional neovascularization into a polymer scaffold and the proliferation, chemoinvasion, and tubulogenesis of ECs [10]. This opposite effect might be mediated through the expression of nitric oxide synthase and the phosphatidylinositol-3 kinase → Akt pathway [10]. It is possible that the antiangiogenic or proangiogenic effect of ginseng extracts depends on the proportion of ginsenosides [1,62].

3.4. Other activities

Other pathways such as those that prohibit the invasion of cancer or reduce inflammatory responses are also reported to be part of the chemopreventive effects of American ginseng. Invasion, which is a crucial aspect of metastasis, involves the migration of cancer cells from an original site to other organs either *via* the bloodstream or lymphatic system [49]. Ginsenoside Rb1 inhibits the chemoinvasion activity of ECs [10]. 20(*S*)-Rh2 prevents the invasion of brain cancer cells *in vitro*, which is attributed to the broad-spectrum inhibition of MMPs [37].

Chronic inflammation is associated with increased cancer risk [49]. Ginseng has been observed to play a role in reducing inflammation [8,63–68], and to suppress colitis through p53-mediated apoptosis of inflammatory cells [8]. IH-901 exerted immunomodulatory and anti-inflammatory effects by deactivating the inflammatory response through inhibition of cyclooxygenase-2 (COX-2) expression [64,65]. 20(*S*)-Rg3 attenuates COX-2 expression, nuclear factor-κB (NF-κB) activation, and activator protein-1 transcription factors [66,67]. 20(*S*)-PPD inhibited inducible nitric oxide synthase and COX-2 expression through inactivation of NF-κB [68].

Multidrug resistance is a major problem in cancer chemotherapy. Overexpression of P-glycoprotein (Pgp) in the plasma membrane of resistant cells extrudes the anticancer drugs and decreases their intracellular accumulation. American ginseng and ginsenosides interfere with the activity of Pgp and thus may improve chemotherapy against human cancers [69,70]. Some ginsenosides showed a chemosensitizing effect on Pgp-mediated multidrug-resistant cells *via* direct interaction with Pgp at the azidopine site [69]. Ginsenoside Rg3 specifically inhibited Pgp-mediated drug accumulation in KBV20C, but not in drug-sensitive cells [70].

A number of previous studies have shown that ginsenosides exhibit cytotoxic effects on a panel of malignant cells in a concentration- and time-dependent manner, but few have evaluated the toxicity of ginsenosides on non-cancer cells or in *in vivo* models. Normal epithelial cells, organic injuries, and weight loss are often selected to observe toxic effects. Ginsenosides showed low toxicity in normal bronchial epithelial cells [71], no

observable toxicity in organs measured by serum markers [73], and no significant effect on changes in body weight [72]. Further evaluations are needed to determine whether ginsenosides have selective toxicity towards tumor cells and if so, how the selectivity is achieved.

4. Structure–function relationship of ginsenosides

4.1. Number of sugar molecules

The structure–function relationship of sugar number and position in ginsenosides with their anticancer potential is outlined in Table 1. Sugar molecules within a ginsenoside have an inverse impact on tumor cells. Anticancer activities increase with the decrease of sugar number. Ginsenosides with four or more sugar molecules (e.g., Rb1 and Rc) show no significant antiproliferative effects [55,74]. Rd with three sugar molecules weakly inhibits the growth of cancer cell [75]. Ginsenosides Rg3 (two sugars), Rh2 (one sugar), IH-901 (one sugar), PPT (no sugar) and PPD (no sugar) inhibit different types of cancer cells [34,39,57,72–74,76,77] and produce synergistic effects with conventional chemotherapy agents [40,52]. Rh2, IH-901 and PPD have 5 to 15-fold relatively stronger antiproliferative effects than does Rg3 [39,57]. Among these compounds, PPD shows the most potent anticancer activity [40,57], suggesting that PPD is a candidate for structural modification [78]. Our recent unpublished observation showed that introducing acetyl groups at selected positions increases the anticancer activity of PPD. Neoglycorandomization to form a library of neoglycosides might enhance tumor-specific accumulation and anticancer properties [79]. Improved anticancer potential might also be expected if heteratoms like nitrogen and sulphur atoms are integrated into the steroid core structure or on the side chain.

That the anticancer effects are inversely related to the number of sugars, i.e., ginsenosides with less or no sugar moieties possess stronger anticancer potential, may be attributed to the following several factors. The hydrophobic character of ginsenosides influences drug absorption. The cellular uptake ratios of ginsenosides on cancer cells decrease with the increase of sugar numbers [80]. A related liner relationship was observed between Log Ps (referred to as the lipophilicity of certain compound) and Log IC_{50} (IC_{50}, 50% inhibitory concentration) of ginsenosides [74]. Like phytosterols, ginsenosides act through specific membrane proteins or by passing directly into the nucleus. The presence of sugar moieties reduces the hydrophobic character of the compounds and decreases the permeability of cell membranes. Because interaction with cell membranes declines, so do the anticancer effects.

4.2. Sugar linkage at C-6

As shown in Table 1, differences in sugar linkage positions may influence biological responses. Most of the anticancer saponins already identified are derived from the PPD group rather than PPT group, which is characterized by a sugar moiety attachment at the C-3 or C-6 position. The C-6 substituent differentiates the two groups of ginsenosides structurally. Ginsenoside Rh2 (PPD type) and Rh1 (PPT type), which possess a glucose linkage at C-3 and C-6 respectively, have similar chemical structures, but the anticancer effect of Rh2 is stronger than that of Rh1 [57]. F1 (20-*O*-glc-PPT) and Rh1 (6-*O*-glc-PPT) have the same number of sugar moieties and the same molecular weight, with different glucose attachment positions at C-20 and C-6 respectively. Cancer cell inhibition by F1 is significantly greater than by Rh1 [74].

With a sugar substitute at C-6, the anticancer activity of ginsenosides is attenuated compared to activity with linkages at C-3 or C-20. Molecular modeling and docking confirm that any sugar moiety at C-6 increases the steric hindrance of these molecules to target proteins [81]. Steric hindrance blocks entrance into the extracellular binding pocket for binding to their targets, thus significantly reducing the anticancer activities of ginsenosides.

4.3. Hydroxyl groups

Since polar substances interact with phospholipid head groups in the hydrophilic domain of the membrane, the insertional orientation of ginsenosides into membranes is influenced by the number and site of polar hydroxyl groups [1]. Differences in the number and position of hydroxyl groups influence pharmacological activity [1]. Elimination of the double bond at C-24/25 and addition of hydroxyl or methoxyl at C-25 increases the anticancer potential of ginsenosides. The anticancer activities of 20(*S*)-25-OCH_3-PPD, 20(*S*)-25-OH-PPD, 20(*S*)-PPD, 20(*S*)-Rh2 and 20(*S*)-Rg3 have been systematically compared. 20(*S*)-25-OCH_3-PPD and 20(*S*)-25-OH-PPD show the most antiproliferative, pro-apoptotic, cell cycle regulatory and inhibitory effects of tumor growth *in vivo* [72,88]. 20(*S*)-25-OCH_3-PPD and 20(*S*)-25-OH-PPD appear to be promising candidates for further development as novel anticancer agents.

Table 1
Possible structure–function relationship of ginsenosides against cancer.

	Ginsenoside	Sugar moieties				Activity	References
		No.	Position				
			C3	C6	C20		
PPD	Rb1	4	2	0	2	Not reported	[55,82]
	Rc	4	2	0	2	Not reported	[13,74]
	Rb2	4	2	0	2	Not reported	[55,74]
	Rb3	4	2	0	2	Not reported	[13,83]
	Rd	3	2	0	1	Possible	[39,75]
	Rg3	2	2	0	0	Low	[34,39,57]
	Rh2	1	1	0	0	Middle	[57,73,84]
	IH-901	1	0	0	1	Middle	[15,16,76]
	PPD	0	0	0	0	High	[39–41]
PPT	Re	3	0	2	1	Not reported	[13,82]
	Rg1	2	0	1	1	Not reported	[28,39]
	Rg2	2	0	2	0	Possible	[39,83]
	Rh1	1	0	1	0	Possible	[85,86]
	F1	1	0	0	1	Low	[39,87]
	PPT	0	0	0	0	Middle	[41,57,77]

PPD, protopanaxadiol group; PPT, protopanaxatriol group. In general, anticancer activity is inversely correlated to the number of sugars. Sugar linkage positions also affect the activities (see text).

On the other hand, dehydration at C-20 increases the bioactivities of ginsenosides. Rg5 differs from Rg3 only by the presence of a hydroxyl group at C-20 in Rg3. Rg5 is stronger at hydroxyl scavenging [33], inhibiting platelet aggregation [89], and is approximately four times more effective than Rg3 at anti-proliferation [38,47,90]. Rh3, however, is a dehydration product at C-20 of Rh2; both Rh2 and Rh3 induce differentiation of promyelocytic leukemia HL-60 cells, but the potency of Rh2 seems to be higher [84].

4.4. Stereoselectivity of 20(S) and 20(R)

20(*S*) and 20(*R*) are stereoisomers of each other that depend on the position of the C-20 hydroxyl in ginsenosides. 20(*S*)-OH is geometrically close to the C-12 hydroxyl of ginsenosides. 20(*R*)-OH is far from the C-12 hydroxyl. The different stereochemistries of the 20(*R*)- and 20(*S*)-ginsenosides produce different pharmacological effects. 20(*S*)-Rg3 scavenges hydroxyl radicals better than does 20(*R*)-Rg3 [91]. 20(*S*)-Rg3 is better aligned with the hydroxyl acceptor group in the ion channels than is 20(*R*)-Rg3, making 20(*S*)-Rg3 an efficient regulator of voltage-dependent ion channel [92]. Voltage-sensitive ion channels play a significant role in the progression of cancer [93]. 20(*S*)-Rg3, 20(*S*)-Rh2 and 20(*S*)-PPD also show stronger chemopreventive effects than their 20(*R*)-sterioisomers [39,94,95]. Because the C-20 hydroxyl group is closer to the C-12 hydroxyl in 20(*S*), stereoselective interactions with lipid membranes may affect the antiproliferative activity by 20(*R*)- and 20(*S*)-ginsenosides.

Though a limited effect against cancer was observed, 20(*R*)-Rh2 inhibits osteoclast formation better than does 20(*S*)-Rh2 [95]. Similarly, although 20(*R*)-Rg3 does not exert appreciable direct effects on the proliferation cancer cells, it inhibits cancer cell invasion and metastasis [34]. It is possible that the antitumor properties of 20(*R*) ginsenosides are in part mediated through the angiosuppressive activity [34,35]. These observations imply that the stereostructure of the C-20 hydroxyl may influence the biological and pharmacological effects of ginsenosides.

5. Summary and perspectives

Ginsenosides possess diverse chemical structures. This diversity is enriched as novel ginsenosides are continually being isolated and identified with improved techniques. Ginsenosides also can be transformed to other compounds by steaming treatment. It is possible that the ginsenoside family is expanded through identification of new compounds from similar genus such as *Oplopanax* [96,97].

With respect to the anticancer effects and mechanisms of ginsenosides, it appears that several molecular mechanisms exist and collectively converge on various signaling pathways. These pathways are not only in cancer cells but also in endothelial and other non-cancer cell types that make the tissue carcinogenesis environment. Some mechanisms have been discovered and far too many more may be unknown. Because the bioavailability of ginsenosides is low, their plasma concentrations may be insufficient to reach to the effects observed under *in vitro* experimental conditions [44,60]. The transformation of ginsenosides by the gut further complicates the prediction of ginseng's clinical effectiveness. Due to these limitations, *in vivo* preclinical models are essential for evaluation and prediction of the clinical effectiveness of the ginseng constituents.

We propose that the number of sugar molecules, structure of hydroxyl groups and stereoselectivity in ginsenosides affect their anticancer activity. These relationships provide useful information for modifying ginsenoside structure. Chemical modifications are an effective way to establish a library of novel compounds that may increase the anticancer activity of ginsenosides [98,99]. Our ongoing experiments show that acetylation of PPD increases its activity. Although C-20 side-chains in ginsenosides are numerous in American ginseng [18,19], their potential effects have not been quantitatively compared. Cancer chemopreventive and therapeutic effects may be enhanced when heteratoms like nitrogen and sulphur atoms are integrated into ginsenosides by syntheses. Further investigations are needed to increase insights into interactive chemical and pharmacological approaches to develop novel oncology agents in drug discovery.

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