Review Article

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Chemical Diversity of *Panax ginseng*, *Panax quinquifolium*, and *Panax notoginseng*

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The major commercial ginsengs are *Panax ginseng* Meyer (Korean ginseng), *P. quinquifolium* L. (American ginseng), and *P. notoginseng* (Burk.) FH Chen (Notoginseng). *P. ginseng* is the most commonly used as an adaptogenic agent and has been shown to enhance physical performance, promote vitality, increase resistance to stress and aging, and have immunomodulatory activity. These ginsengs contain saponins, which can be classified as dammarane-type, ocotillol-type and oleanane-type oligoglycosides, and polysaccharides as main constituents. Dammarane ginsenosides are transformed into compounds such as the ginsenosides Rg_3, Rg_5, and Rk_1 by steaming and heating and are metabolized into metabolites such as compound K, ginsenoside Rh_1, proto- and panaxatriol by intestinal microflora. These metabolites are nonpolar, pharmacologically active and easily absorbed from the gastrointestinal tract. However, the activities metabolizing these constituents into bioactive compounds differ significantly among individuals because all individuals possess characteristic indigenous strains of intestinal bacteria. To overcome this difference, ginsengs fermented with enzymes or microbes have been developed.

Keywords: *Panax ginseng*, *Panax quinquifolium*, *Panax notoginseng*, Constituents, Biotransformation

INTRODUCTION

The term ginseng refers to the dried roots of several plants of the species Panax sp. (Family Araliaceae). The three major commercial ginsengs are *P. ginseng* Meyer (Korean ginseng), which has been used as an herbal medicine for more than 2000 years [1], *P. quinquifolium* L. (American ginseng), and *P. notoginseng* (Burk.) FH Chen (Notoginseng) [2,3]. These ginsengs have been used worldwide for thousands of years as either food or herbal medicines. *P. ginseng* has been the most commonly used as an adaptogenic agent and has been shown to enhance physical performance, promote vitality, increase resistance to stress and aging, and have immunomodulatory activity [4,5].

The roots of these ginsengs have been used as herbal medicines in Asian countries, and their bioactive chemicals have been isolated. In 1854, Garriques performed the first chemical studies on ginseng [6] and separated a saponin fraction from *P. quinquifolium*. Despite these findings, the components of ginseng were not studied again until 1963. Shibata *et al*. [7], Shibata *et al*. [8], and Shibata *et al*. [9] isolated ginseng saponins from the root of *P. ginseng* and identified their structures in 1963. These saponins were called ginsenosides. Since the reports of Shibata *et al*., many researchers have isolated the components of Korean ginseng, American ginseng, and Notoginseng. Today, approximately 200 substances, such as ginsenosides, polysaccharides, polyacetylenes, peptides, and amino acids, have been isolated from Korean gin-

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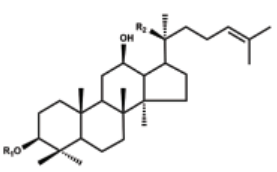
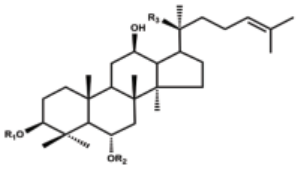


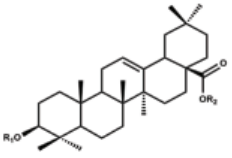
PPD

	R1	R2
Ginsenoside Rb_1	Glc-glc-	Glc-glc-O-
Ginsenoside Rd	Glc-glc-	Glc-O-
Ginsenoside Rg_3		HO-
Ginsenoside Ra_3	Glc-glc-	Xyl-glc-glc-
Ginsenoside Rh_2	Glc-	HO-
Compound K	H	Glc-O-
20S-protopanaxadiol	H	HO-



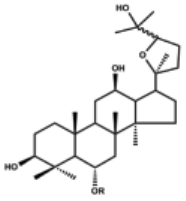
PPT

	R1	R2	R3
Ginsenoside Re	H		
Ginsenoside Rg_1	H	Glc-	Glc-O-
Ginsenoside Rf	H	Glc-glc-	HO-
Ginsenoside Rh_1	H	Glc-	HO-
Notoginsenoside R1	H	Xyl-glc-	Glc-O-
Gisnenosdie F1	H	H	Glc-O-
20S-protopanaxatriol	H	H	OH



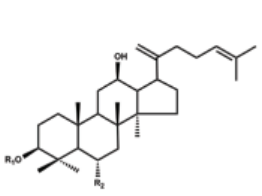
Oleanane

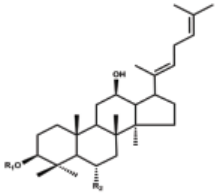
	R1	R2
Ginsenoside Ro	GlcA-glc-	Glc-
Chikusetsusaponin IVa	GlcA-	Glc-



Octotillol

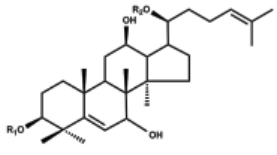
	R
Majonoside R2	Xyl-glc-
Pseudogiinsenoside RTt5	Glc-

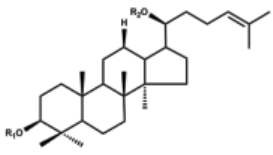




Modified PPD and PPT

	R1	R2		R1	R2
Ginsenoside Rk_1	Glc-glc-	H-	Ginsenoside Rg_5	Glc-glc-	H
Ginsenoside Rk_2	Glc-	H	Ginsenoside Rh_3	Glc-	H
Ginsenoside Rk_3	H	Glc-O-	Ginsenoside Rh_4	H	Glc-O-





Modified ginsenoside

	R1	R2		R1	R2
Quinquinoside IV	Glc-glc-	Glc-glc-	Vina-ginsenoside R3	Glc-glc-	Glc-
Notoginsenoside G	Glc-glc	Glc-			

Fig. 1. The structures of representative ginseng saponins. PPD, protopanaxadiol; PPT, protopanaxatriol.

seng [2], and more than 100 substances have been isolated from American ginseng and Notoginseng. Among the substances isolated from ginseng, the major and most unique components are the ginseng saponins (ginsenosides), which can be classified as dammarane-type, ocotillol-type and oleanane-type oligoglycosides (Fig. 1), and polysaccharides [10]. Furthermore, the dammarane-type saponins are classified into protopanaxadiol and protopanaxatriol types. The protopanaxadiol-type has sugar moieties attached to OH at C-3 and/or C-20, and the protopanaxatriol-type has sugar moieties attached to OH at C-3, C-6, and/or C-20. The ocotillol-type has a five-membered epoxy ring at C-20, and the oleanane-type has a modified C-20 side chain. With the development of instrumental analysis, minor constituents are constantly being isolated from these ginsengs.

Chemically, several differences exist among Korean ginseng, American ginseng, and Notoginseng. An important parameter used for differentiation is the presence of the ginsenoside Rf in Korean ginseng and Notoginseng, the pseudoginsenoside F11 in American ginseng [11], and the notoginsenoside R1 in Korean ginseng and Notoginseng. In addition, the ratio of Rg_1/Rb_1 has been widely used to differentiate between these ginsengs. Ratios of less than 0.4 are indicative of American ginseng, whereas a high value ratio is characteristic of Korean ginseng and Notoginseng [12]. Although notoginsenosides are not isolated from the root of Korean ginseng, many notoginsenosides are found in Notoginseng (Table 1).

Recent studies have reported the constituents of the roots of Korean ginseng, American ginseng and Notoginseng as well as their leaves and stem, flower buds, and fruits. Based on these findings, the leaves and stem, flower buds, fruits, and roots have recently been used as functional food, cosmetics, and herbal medicines. Furthermore, immunopotentiating polysaccharides have been isolated from these ginsengs. Acidic polysaccharides are more abundant in Korean ginseng compared with those in American ginseng and Notoginseng. However, the structures of many polysaccharides that are isolated from ginsengs have not been clearly identified.

CHEMICAL DIVERSITY OF *PANAX GINSENG*

Today, approximately 200 substances, such as ginsenosides, polysaccharides, polyacetylenes, peptides, and amino acids, have been isolated from Korean ginseng [2]. Of these, ginsenosides and polysaccharides are the major and most unique constituents.

Saponins

Saponins are the major constituents isolated from the root of Korean ginseng. Because *P. ginseng* has been historically used as an herbal medicine, extensive chemical studies have focused on the root of *P. ginseng*. Recent studies are focusing on the constituents of the leaves and stem, flower buds, fruits, and roots of ginseng and their pharmacological activities. Since Shibata *et al*. isolated prosapogenins in 1963, many kinds of saponins have been isolated from its roots, leaves and stem, flower buds, fruits, and seeds. Shibata *et al*. [7] established the chemical structures of main the prosapogenins 20S-protopanaxadiol, 20S-protopanaxatriol, prosapgenin, and ginsenoside Rg_1, which were extracted from the dried root of ginseng [8,9,13]. Kitagawa *et al*. [14] and Kitagawa *et al*. [15] isolated malonyl ginsenosides Rb_1, Rb_2, Rc, and Rd from the dried root of ginseng. Subsequently, the ginsenosides Ro, Ra_1, Ra_2, Ra_3 Re, Rf, Rg_1, Rg_2, Rg_3, Rh_1, the notoginsenosides R4, 20-gluco-ginsenoside Rf, koryoginsenoside R1, and R2, and the ginsenosides Rb_1, Rb_2, Rc, and Rd, have been reported [11,16].

Recently, Ruan *et al*. [17] isolated the malonylginsenoside Ra_3 from the root of *P. ginseng*. Zhu *et al*. [18] isolated 6 new protopanaxatriol-type ginsenosides, the ginsenosides Re_1, Re_2, Re_3, Re_4, Re_5, Re_6, and 10 known protopanaxatriol ginsenosides, including the ginsenoside Rg_1 from the root of *P. ginseng*.

Approximately one thousand years ago, red (steamed) ginseng was developed to enhance the storage and the pharmacological effect of ginseng in Korea. Until recently, red ginseng had been widely made and largely consumed. Many scientists have isolated and identified its constituents to understand the pharmacological activities and bioactive components of red ginseng.

Table 1. Comparison of typical ginsenoside composition of Korean ginseng (*Panax ginseng*), American ginseng (*P. quinquefolius*) and Notoginseng (*P. notogisneng*)

Chemical composition	Korean ginseng	American ginseng	Notoginseng
Major ginsenosides	Rb_1, Rg_1, Rb_2	Rb_1, Re, Rd	Rb_1, Rg_1, Ra_3, R1
PPD-group to PPT-group	<2.0	>2.0	<2.0
Rb_1: Rg_1	<5.0	>5.0	<1

PPD, protopanaxadiol; PPT, protopanaxatriol.

Hiromichi *et al*. [19] isolated the ginsenosides Ra_1, Ra_2, and Ra_3, and the notoginsenoside R4 from the steamed root of ginseng (red ginseng). Kasai *et al*. [20] isolated the ginsenosides Ra_1, Ra_2, Ra_3, Rs_1, and Rs_2, the notoginsenoside R1, and the quinquenoside R1. Thereafter, the ginsenosides Ro, Rb_1, Rb_2, Tc, Rd, Re, Rf, Rg_1, Rg_2, Rg_3, Rh_1, the ginsenosides Rh_2, 20R-ginsenoside Rh_1, 20S-ginsenoside Rg_3, and 20R-ginsenoside Rg_2 were isolated from red ginseng. Ryu *et al*. [21] isolated the ginsenoside Rg_6 and 20(E)-ginsenoside F4 from red ginseng. Baek *et al*. [22] isolated the ginsenoside Rh_4. Then, the ginsenosides Rs_1, Rs_2, Rs_3, and Rs_4, the quinoginsenoside R4, the ginsenosides Rg_3, Rg_5, Rg_6, F4, and Rf_2 were isolated from red ginseng [23,24]. In particular, large quantities of the ginsenosides Rh_1, Rg_3 and Rg_2 were found in red ginseng. Under intense steaming or heating, ginsenoside Rg_3 may be further transformed to 20S-Rh_2 and 20R-Rh_2, and these ginsenosides subsequently become aglycone 20S-protopanaxadiol, 20R-protopanaxadiol, or even 20-dehydroprotopanaxadiol through chemical degradation. Ginsenosides Rk_1 and Rg_5 are again transformed into the degradation products Rk_2 and Rh_3. Rh_1 can be changed into the aglycones 20S-protopanaxatriol, 20R-protopanaxatriol, and 20-dehydropropanaxatriol.

Shoji *et al*. [25] and Shoji *et al*. [26] were interested in the constituents of the leaves of *P. ginseng*. They isolated the ginsenosides Rb_1, Rb_2, Rc, Rd, Re, Rg_1, F1, F2, and F4 from the leaves and stems. The ginsenosides F4, 20R-protopanaxadiol, 20R-protopanaxatriol, ginsenoside Rh_3, 20R-ginsenoside Rh_2, 20S-ginsenoside Rh_2, ginsenosides Rh_1, Rg_3, Rg_2, Rg_1, Re, Rd, Rc, Rb_2, and Rb_1 were isolated from the flower buds of *P. ginseng* [27]. Ginsenosides Rh_5, Rh_6, Rh_7, Rh_8, Rh_9 and Rg_7, the majoroside F1, F2, the notoginsenoside Fe, the majoroside F4, and chikusetsusaponin L8 were also isolated [28,29].

Recently, Tung *et al*. [30] isolated two new ginsenosides Ki and Km from the leaves of *P. ginseng*. Liu *et al*. [31] isolated three new ginsenosides, 20S-3β,6α,12b-,20-tetrahydroxydammara-25-ene-24-one 20-*O*-β-glucopyranoside, 20S-3β,6α,12β-,20,24,25-pentahydroxydammarane 20-*O*-β-D-glucopyranoside, 20S,23E-3β,6α,12b,20,25-tetrahydroxydammara-23-ene 20-*O*-β-glucopyranoside and six known compounds from the leaves of *P. ginseng*. Wu *et al*. [32] isolated 3β,6α,12β-triol-22,23,23,25,26,27-hexanordammaran-20-one and dammar-20(22),24-diene-3β,6α,12β-triol from the leaves of *P. ginseng*. Huang *et al*. [33] isolated new 20R,22(xi),24(S)-dammar-25(26)-ene-3β,6α,12β,20,22,24-hexanol from the leaves of *P. ginseng* [34]. Tung *et al*. steamed the leaves of *P. ginseng*, and then investigated their constituents. They isolated new ginsenosides: SL-1, SL-2, SL3, and 11 known compounds [35].

Shoji *et al*. [26] also investigated the constituents of the flower buds of *P. ginseng*. They isolated ginsenosides

Rb_1, Rb_2, Rc, Rd, Re, Rg_1, F3, and M7cd from the flower buds of *P. ginseng*. They also isolated ginsenosides Rb_2, Rd, Rd, Re, Rg_2, 20R-protopanaxatriol, 20R-ginsenoside Rh_1, 20R-ginsenoside Rg_2, notoginsenoside-E, and gypenoside XVII from the flower buds of *P. ginseng* [25]. Yoshikawa *et al*. [36] isolated new floralginsenosides A, B, C, D, E, and F from the flower buds of *P. ginseng*. They also isolated new floralginsenosides-M, N, O, and P and the ginsenosides Rd and Re [37]. Nguyen *et al*. [38] isolated new floralginsenosides-Ta, Tb, Tc, and 6 known dammarane-type saponins from the flower buds of *P. ginseng*. Tung *et al*. [39] isolated antioxidant floralginsenosides Ka, Kb, and Kc from the flower buds of *P. ginseng*. Floralginsenosides Ka-Kc and majoroside F1 were also isolated from the flower buds of *P. ginseng* [39]. Recently, many researchers have been interested in the fruits and seeds of *P. ginseng*. Zhao *et al*. [40] isolated three new ginsenosides, 20R-25 methoxyl-dammarane-3β,6α,12β,20-triol, 20R-25-methoxyl-dammarane-3β,6α,12b,20-tetrol, and 20R-20,25 dimethoxyldammarane-3β,6α,12b,20-diol, and 2 known ginsenosides from the fruit of *P. ginseng*. Sugimoto *et al*. [41] isolated a new type of saponin, called panaxadione, from the seeds of *P. ginseng*.

Polysaccharides

Many kinds of polysaccharides have been isolated from Korean ginseng. For example, Konno *et al*. [42], Konno *et al*. [43], and Ohshima *et al*. [44] isolated the hypoglycemic glycans, panasans A - E, poanaxans F - H, panaxans I - L, panaxans M - P, and panaxans Q - U from the root of *P. ginseng*. Tomoda *et al*. [45] and Tomoda *et al*. [46] isolated the immunomodulating glycans ginsenan PA and ginsenan PB from the root of *P. ginseng*. These immunomodulationg glycans are composed of L-arabinose, D-galactose, L-rhamnose, Dgalacturonic acid, and D-glucuronic acid. However, the intact structures of these glycans have not been identified. Immunomodulating glycans, such as acidic polysaccharide ginsenan S-IA and ginsenan S-II A (MW 5.6×10^4, 1.0×10^5), have been continually reported.

Others

Favonoids and polyacetylenes, such as kaempferol, trifolin and panasenoside, were also isolated from the roots

of *P. ginseng*. Matsunaga *et al*. [47] isolated polyacetylenes, panaxynol, and panaxydol.

Iwabuchi *et al*. [48] isolated two sesquierpene alcohols, pansinsanol A and panasinsanol B. Sesquiterpene hydrocarbons, α-panasinene, β-panasinsene, α-neoclovene, and β-panasinsene were also isolated from the rootlet. Furthermore, two new sesquitene alcohols, ginsenol and senecrassidiol, were found [49,50]. In addition, ginsenoynes A, B, C, D, E, F, G, H, I, J, and K have been reported.

CHEMICAL DIVERSITY OF *PANAX QUINQUIFOLIUM*

American ginseng (*P. quinquifolium* L., family Araliaceae), a plant native to North America, is now cultivated in many countries. *P. quinquifolium* also contains saponins, flavonoids, polyacetylenes, polysaccharides, amino acids, fatty acids, and peptides.

Saponins

Saponins, particularly ginsenosides, are constituents of American ginseng (*P. quinquifolium*). More than 60 ginsenosides, including dammarane-, ocotillol-, and oleanane-types, have been isolated from the roots, leaves, stems, flower buds and berries of *P. quinquifolium*. Chen *et al*. [51] isolated quiquenosides L10 and L16 from the leaves and stems of *P. quinquifolium*. Jiang *et al*. [52] isolated two new saponins, 3β,12β,20S trihydroxydammar-23-ene-3-*O*-{[β-D-glucopyranosyl(1->2)-β-D-glucopyranosyl]-20-*O*-[α-L-arabinopyranosyl(1->)]-β-D-glucopyranoside and 3β-20S-dihydroxy-12β-23R-epoxydammar-24-ene-3-*O*-{[β-D-glucopyranosyl(1->2)-β-D-glucopyranosyl]-20-*O*-[β-D-xylosyl(1->6)]-β-D-glucopyranoside from the leaves of *P. quinquifolium*. Many ginsenosides have been isolated from *P. quinquifolium*. Protopanaxadiol-type ginsenosides isolated from the roots, leaves and stems, and flower buds of American ginseng are the ginsenosides Rb_1, Rc, Rb_2, Rb_3, Rd, Rg_3, F2, Rs_1, quinquenosides I, II, III, V, L10, L14, pseudoginsenosides RC1, F8, and gypenoside XVII [51-56]. Protopanaxatriol-type ginsenosides found in American ginseng are the ginsenosides Rg_1, Rg_2, Re, Rg_2, F3, Ia, F1, Rh_1, 20S-acetyl ginsenoside Rg_2, 20R-acetyl ginsenoside Rg_2, floralquinquenoside E, 20R-ginsenoside Rg_2, Rh_1, 20S-protopanxatriol, and 20R-protopanaxatriol [52,54,56]. Du *et al*. [57] isolated four malonyl-ginsenosides, Rb_1, Rc, Rb_2, and Rd. In addition, the minor ginsenosides 4 ocotillol-type ginsenosides (24Rpseudoginsenoside F11, pseudoginsenoside RT5, F-11, 24R-vina-ginsenoside R1), 2 oleanane-type ginsenosides (ginsenoside Ro, chikusetsusaponin Iva), and 3 dammarane saponins with a modified steroid skeleton (vinaginsenoside R3, quinquenoside IV, and notoginsenoside G) were isolated from *P. quinquifolium* [54,56]. Minor saponins modified in C-20 side-chain (quinquenosides L1, L2, L8, L11, L3, L7, L9, L16, I, gypenosides LXIX, LXXI, majoroside-F1, notoginsenosides A, C, E, K, ginsenosides I, III, vina-ginsenoside R8, floralquinquenosides B, D, A, C, quinquefolosides La, Lc) were also isolated [52,54,58]. American red ginseng was also experimentally prepared under the same steam and heat treatments as Korean ginseng [59]. Then, the chemical composition of American red ginseng was studied. The constituents of the steamed American ginseng were largely different from those of the untreated ginseng. The steaming process induced obvious chemical degradation and conversion of original saponins to some newly occurring compounds. The polar ginsenosides, including Rg_1, Re, Rb_1, Rc, Rb_2, Rb_3, and Rd, decreased remarkably; however, less polar ginsenosides, including Rg_2, Rg_3, Rg_5, Rh_2, Rk_1, and Rs_4, increased [60,61]. The 20S and 20R-ginsenoside are typical stereoisomers formed by the selective attack of the hydroxyl group after elimination of the glycosyl residue at C-20. Additionally, Rk_1/Rg_5 and Rk_3/Rh_4, isomers of the double bond at C-20/21 or C-20/22, were identified. This result was similar to the transformation of ginsenosides seen in Korean red ginseng.

Nakamura *et al*. [54] isolated five new dammarane-type triterpene glycosides, floralquinquenosides A, B, C, D, and E, and 18 known dammarane-type triterpene glycosides, ginsenoside Rb_3, ginsenoside Rd, ginsenoside Rs_1, pseudo-ginsenoside-RC1, pseudo-ginsenoside-F8, quinquenoside III, ginsenoside I, notoginsenoside-E, ginsenoside Re, ginsenoside Rg_1, ginsenoside Rg_2, ginsenoside-F3, ginsenoside Ia, quinquenoside L9, pseudo-ginsenoside RT5, pseudo-ginsenoside F11, and 24(S)-pseudo-ginsenoside F11 from the flower buds of *P. quinquifolium* L. Qiu *et al*. [62] isolated a new saponin quinquefoloside-L(c) (3β,12β,20Strihydroxy-25-methoxy-25-methoxydammar-23-ene-3-*O*-β-D-glucopyranosyl(1->2)β-D-glucopyranosyl-20-*O*-β-xylopyranosyl(1->6)-β-D-glucopyranoside) from the leaves of *P. quinquifolium*. This saponin was found to be cytotoxic against tumor cells.

Polysaccharides

Many kinds of polysaccharides were also isolated from American ginseng. Immunomodulating glycans, such

as water-soluble COLD-FX (CVT-E002), were isolated from the roots of *P. quinquifolium* [63]. These glycans are poly furanosyl-pyranosylsaccharides. Hypoglycemic glycans, such as quinquefolans A, B, and C, were isolated from the roots of *P. quinquifolium* [64]. These glycans displayed hypoglycemic effects in normal and alloxan-induced hyperglycemic mice.

Others

Polyacetylenes, such as polyacetylene PQ-1, PQ-2, PQ-3, panaxynol, panaxydol, and 1,8-heptadecadiene-4,6-diyne-3,10-diol, were isolated from the roots of *P. quinquifolium* [65-67]. Nakamura *et al*. [54] isolated three flavonoids and 3 flavonoid glycosides, kaempferol 3-*O*-β-D-sophoroside-7-*O*-α-Lrhamnopyranoside, kaempferol-*O*-(2,3-di-E-p-coumaroyl-α-L-rhamnopyranoside), and kaempferol-3-*O*-α -L-rhamnopyranoside.

CHEMICAL DIVERSITY OF *PANAX NOTOGINSENG*

Notoginseng is also commonly used as a traditional Chinese medicine. Notoginseng contains saponins, flavonoids, polyacetylenes, polysaccharides, amino acids, fatty acids, and peptides. Ginsenosides and polysaccharides are notable components in *P. notoginseng*, just as they are in *P. ginseng* and *P. quinquifolium* [68,69].

Saponins

More than 60 dammarane saponins have been isolated from the roots, rhizome, rootlets, fibers, leaves, flower

buds, seeds, and fruit pedicels of Notoginseng. Most of these saponins are ginsenosides and notoginsenosides.

However, an oleanolic acid saponin has not been found in Notoginseng. Oleanolic acid saponin occurs commonly in the plant kingdom and can be isolated from both Asian ginseng and American ginseng. The chemical constituents of American ginseng can be distinguished from those of Notoginseng.Yoshikawa *et al*. [70] and Yoshikawa *et al*. [71] isolated 9 dammarane-type triterpene glycosides, notoginsenosides-A, -B, -C, -D, -E, -G, -H, -I, and -J, and an acetylenic fatty acid glycoside, notoginsenic acid β-sophoroside. Chen and Sorensen [72] isolated ginsenosides Rb_1, Rb_2, Rc, Rd, Re, Rf, and Rg. Wei *et al*. [73], Wei *et al*. [74], and Wei *et al*. [75] subsequently reported the isolation of ginsenoside Rb_1, notoginsenosides-Fc and -Fa, and gypenosides XV and XVII. The genuine aglycones of these ginsenosides are hydrolyzed to panaxadiol and panaxatriol (dammar-20(22)-en-3β,12β,26-triol, and 20R-dammaran-3β,12β,20,25-tetrol) by acidic hydrolysis [76]. Cui *et al*. [76] isolated two new ginsenosides, notoginsenoside Rw1 [6-*O*-β-D-xylopranosyl-20-*O*-β-D-xylopyranosyl-(1->6)-β-D-glucopyranosyl-dammar-24-ene-3b,6a,12b,20(S)tetraol] and Rw2 [6-*O*-β-Dxylopyranosyl-(1->2)-β-D-glucopyranosyl-dammar-22-ene-(trans)-3β,6α,12βb,20(S),25-pentaol], from the roots of *P. notoginseng*. Wan *et al*. [77] isolated 5,6-didehydroginsenoside Rd, 5,6-didehydroginsenoside Rb_1 from the root of *P. notoginseng*. Liu *et al*. [78] identified 151 saponins in the root of notoginseng by Esi-Ms, HPLC/ESI-MS(n). Of these, 56 new compounds were identified, although these compounds were not isolated.

Recently, Wang *et al*. [79] isolated 20S-25-methoxyldammarane-3β,12β,20-trio, a compound that exhibits potent cytotoxicity against tumor cells. Zhao *et al*. [80] isolated 20(S)-25-OCH3-protopanaxadiol, another cytotoxic compound against tumor cells, from the leaves of *P. notoginseng*. Wang *et al*. [81] isolated fl oranotoginsenosides-A, B, C, and D and 5 known compounds from the flower buds of *P. notoginseng*.

Sun *et al*. [82] steamed the root of notoginseng and isolated ginsenosides Rg_1, Re, Rb_1, Rd and notoginsenoside R1 from Notoginseng. As seen on the steaming process of red ginseng, steaming notoginseng increased the contents of ginsenosides Rh_1, Rg_2, Rg_3, Rh_2, and 20R-ginsenoside Rg_2. Teng *et al*. [83] treated notoginseng roots under a specific mild acidic condition and isolated twenty saponins from them. Five isolated saponins were new dammarane glycosides, and these saponins were named as notoginsenosides T1-T5. Other saponins were the ginsenosides Rg_5, Rg_2, Rg_1, Re, Rh_4, Rd, 20R-ginsenoside Rg_3, ginsenoside Rg_3, 20R-ginsenoside Rh_1, ginsenoside Rh_1, the notoginsenosides E, R2, and R1, the gypenoside XVII, 20R-25-hydroxyginsenoside Rh_1, and 20S-25-hydroxyginsenoside Rh_1.

Polysaccharides

Sanchinan-A (1.5×10^6), PF3111, PF3112, PBGA11, and PBGA12 were isolated from Notoginseng. These compounds showed immunostimulating activity [84].

Others

Choi *et al*. [85] isolated the β-amyloid-induced neurotoxicity-ameliorating constituent, quercetin-3-β-xylopyranosyl-β-D-galactopyranoside, from the root of Notoginseng. Wei *et al*. [73] isolated quercetin-3-Osophoroside, kaempferol-3-*O*(2”-β-D-glucopyranosyl)-β-D-galactopyranoside, and quercetin-3-*O*(2’’-β-

Dglucopyranosyl)-β-D-galactopyranoside from the leaves of *P. notoginseng*. Liu *et al*. [86] isolated polyacetylene compounds, and Chan *et al*. [87] isolated trilinolein from the roots of *P. notoginseng*.

METABOLITES OF MAIN CONSTITUENTS AND THEIR BIOLOGICAL ACTIVITIES

When ginseng is orally administered to humans, its main constituents (ginseng saponins and polysaccharides) cannot be easily absorbed from the intestine due to their hydrophilicity. Therefore, these constituents inevitably come into contact with intestinal microflora in the alimentary tract and can be metabolized by intestinal microflora [88,89]. The metabolites are then easily absorbed from the gastrointestinal tract because most of the metabolites are nonpolar. These absorbed metabolites may express pharmacological actions. For example, when the extract of the root of *P. ginseng* was orally administered to humans, compound K and ginsenosides Rh_1 and F1 were detected in the blood [90,91]. Ginsenosides Rb_1 and Rb_2 were not detected. When ginsenoside Rb_1, a main constituent of *P. ginseng*, was orally administered to conventional rats, compound K was detected in the intestinal contents, blood, and urine [92,93]. Ginsenoside Rb_1 was not detected. Furthermore, compound K was detected in the blood and intestinal contents when ginsenoside Rb_1 was orally administered to gnotobiotic rats [94]. However, when ginsenoside Rb_1 was orally administered to germ-free rats, compound K and ginsenoside Rb_1 were not detected in the blood and intestinal contents. When Notoginseng extract, whose main constituents are ginsenoside Ra_3, Rb_1, Rd, Re, and Rg_1 and notoginsenoside R1, was orally administered to rats, the compounds that were mainly absorbed into the blood were ginsenoside Ra_2, Rb_1, and Rd and compound K [95]. These results are not consistent. Neverthelse, compound K, a metabolites of protopanaxadiol ginsenosides, always are absorbed into the blood. Furthermore, of parental ginsenosides and their metabolites, compound K, ginsenoside Rh_1, Rh_2, and protopanaxatriol showed the most potent biological effects compared with those of parental compounds. For example, compound K and 20(S)-ginsenoside Rh_2 exhibited the most potent cytotoxicity against tumor cells [96,97]. Ginsenoside Rb_1 and Rb_2 did not exhibit cytotoxicity against the tumor cell lines. However, most ginsenosides have anti-tumor activities *in vivo* [98,99]. Therefore, the metabolism of ginseng constituents by intestinal microflora is likely to play an important role in the pharmacological activity of ginseng. Protopanaxadiol ginsenosides are metabolized to compound K by human intestinal microflora, such as *Bifidobacterium* K-110, *Bifidobacterium* H-1, *Provetellaoris*, *Fusobacterium* K-60, *Bacteroides* JY-6, *Eubacterium* A-44, and *Bifidobacterium* K-506 [89]. Protopanaxatriol saponin ginsenosides Re and Rg_1 were easily transformed to ginsenoside Rh_1 or protopanaxatriol by human intestinal bacteria, such as Fusobacterium K-60, Bacteroides JY-6, Eubacterium A-44, and Bacteroides HJ-15 [100,101].

Compound K

Compound K exhibits chemopreventive [97], chemotherapeutic [102], anti-inflammatory [103], hepatoprotective [92], anti-pruritic [104], antiallergic [105], and hypoglycemic [106] effects in vitro and *in vivo*. Compound K also reduced stress in mice [107].

Ginsenoside Rh_2

Ginsenoside Rh_2 showed anti-tumor [99], anti-inflammatory [108], anti-pruritic [109], antiallergic [106], hepatoprotective [110], hypoglycemic, and hypolipidemic effects in mice [111,102]. Ginsenoside Rh_2 effectively inhibited adipocyte differentiation via PPAR-γ inhibition [112] and improved insulin sensitivity [113]. Ginsenoside Rh_2 ameliorated transient focal ischemia in rats [114].

Ginsenoside Rh_1

Ginsenoside Rh_1 exhibited anti-inflammatory [115], antiallergic [106], anti-dermatitic [116] effects in vitro and *in vivo*. Ginsenoside Rh_1 showed anticarcinogenic and estrogenic effects [117] and stimulated the secretion of lipoprotein lipase in 3T3-L1 adipocytes [118].

Protopanaxatriol

Protopanaxatriol binds to glucocorticoid and estrogen receptors in endothelial cells and stimulates these receptors [119]. Protopanaxatriol (PPT) also has an estrogenic effect in MCF9 cells [120]. PPT has an adjuvant effect and activates PPARγ in 3T3-L1 adipocytes [121]. PPT also exhibits anti-inflammatory and antiangiogenic effects [122].

ACIDIC POLYSACCHARIDES

Ginseng polysaccharides are also degraded to low molecular weights by heat/steaming processing and intestinal microflora. However, the properties of the degraded molecules have not been clearly studied. Water-soluble polysaccharides and oligosaccharides from Korean ginseng have a number of effects on immune and host

Table 2. Ginsenosides transformation by hydrolyzing the sugar moieties in ginsenosides using microbial glycosidases

Substrate	Product	Microorganism	Enzyme	Reference
Ginseng extract	C-K	*Bifidobacterium longum H-1*	β-D-Glucosidase/α-L-Arabinosidase	[131]
Ginseng extract		*Sulfolobus solfataricus*	β-D-Glycosidase (recombinant: 83)	[132]
Ginseng extract		*Aspergillus niger*	Pectinase (commercial)	[133]
Ginseng extract	Rh_2	*Bifidobacterium longum H-1*	β-D-Glucosidase (crude)	[134]
Ginseng extract	Rg_3	*Trichoderma reesie*	Cellulase (commercial)	[135]
Ra_1, Ra_2	Rb_2, Rc	*Bifidobacterium breve*	β-D-Xylosidase (purified)	[136]
Gypenoside-5	Rd	*Absidia* sp.	α-L-Rhamnosidase (purified)	[137]
Rb_2		*Bifidobacterium breve*	α-L-Arabinopyranosidase (purified)	[138]
Rc		*Bifidobacterium breve*	α-L -Arabinopyranosidase (purified)	[136]
Rb_1		*Chloroflexus aurantiacus*	β-D-Glucosidase (recombinant)	[139]
Rb_1		*Cladosprorium fulvum*	β-D-Glucosidase (purified)	[140]
Rb_1, Rb_2, Rc		*Thermus caldophilus*	β-D-Glycosidase (recombinant)	[141]
PPD mixture		*Trichoderma viride*	Cellulase (commercial)	[142]
Rb_1, Rb_2, Rc	Rg_3	*Penicillium* sp.	Lactase (commercial)	[143]
Rb_1, Rd		*Paecilomyces bainier*	β-D-Glucosidase (purified)	[144]
Rb_1, Rb_2, Rc	F_2	*Aspergillus oryzae*	Lactase (commercial)	[142]
Rb_1, Rb_2, Rc		*Penicillium* sp.	Lactase (commercial)	[143]
Rb_1, Rb, Rc	C-K, C-Y, C-Mc	*Sulfolobus acidocaldarius*	β-D-Glycosidase (recombinant)	[132]
Rb_1, Rb, Rc,		*Paecilomyces bainier*	β-D-Glucosidase (purified)	[145]
Rb_1	C-K	*Fusobacterium* sp.	β-D-Glucosidase (purified)	[146]
Rb_1, Rb_2, Rc		*Aspergillus oryzae*	β-D-Galactosidase (commercial)	[142]
Rb_1, Rb_2, Rc		*Penicillium* sp.	Lactase (commercial)	[143]
Rb_1, Rb_2, Rb_3, Rc		*Aspergillus* sp.	β-D-Glycosidase (purified)	[147]
Rg_3	Rh_2	*Fusarium proliferatum*	β-D-Glucosidase (purified)	[148]
Re	Rg_1	*Penicillium* sp.	Hesperidinase (commercial)	[143]
Re		*Bacterodies* sp.	α-D-Rhamnosidase (purified)	[149]
Re	Rg_2	*Aspergillus oryzae*	β-Galactosidase (commercial)	[142]
Re		*Bacterodies* sp.	β-D-Glucosidase (purified)	[150]
Rg_1	F_1	*Bacterodies* sp.	β-D-Glucosidase (purified)	[150]
Re, Rg_1		*Penicillium decumbens*	Naringinase (commercial)	[142]
Rg_1	Rh_1	*Bacterodies* sp.	β-D-Glucosidase (purified)	[150]
Rg_2		*Aspergillus oryzae*	β-Galactosidase (commercial)	[143]
Rg_2		*Absidia* sp.	α-L -Rhamnosidase (purified)	[151]
Rg_1, Rg_2, Rf		*Penicillium* sp.	Lactase (commercial)	[143]
Rf		*Aspergillus niger*	β-D-Glucosidase (recombinant)	[152]

C-K, compound K; PPD, protopanaxadiol; C-Mc, compound Mc; C-Y, compound Y.

defense functions [123]. These glycans activate macrophages, induce IFN-γ and TNF-α production in immune cells, stimulate phagocytosis [124], stimulate natural killer-cell activity [125], and activate components of cell-mediated immunity [126]. Red ginseng acidic polysaccharides restored the proliferation of splenocytes and NK cell activity that had been suppressed by paclitaxel. Additionally, the synergistic effect of RGAP and paclitaxel increased the tumoricidal activity of macrophages [127]. Antirotaviral pectic polysaccharide was isolated from heat-processed ginseng [128].

Industrial application

When ginseng is orally administered to humans, its hydrophilic components inevitably come into contact with intestinal microflora in the alimentary tract and undergo transformation prior to absorption from the gastrointestinal tract. The pharmacological activities of these compounds are then expressed.

All individuals possess characteristic indigenous strains of intestinal bacteria. The activities that metabolize these constituents into bioactive compounds that are absorbable from the intestine into the blood differ significantly between individuals. Ginsengs containing bioactive and absorbable metabolites are valuable for treating various diseases. Therefore, fermented and heat-processed ginseng products have recently been released onto the market. Fermentation and heat processing transform hydrophilic components to hydrophobic compounds that can be easily absorbed from the gastrointestinal tract. To develop fermented ginseng, edible microbes, such as probiotics, should be used. Currently, there are few developed fermented ginsengs.

Therefore, research related to the biotransformation of ginsenosides is focused on bioactive production.

These metabolites, such as ginsenoside compound K, Rh_1, Rh_2, Rk_1, Rh_3, Rh_4, and protopanaxadiol, are readily absorbed into the blood and express pharmacological effects. These ginsenosides have demonstrated excellent potential for pharmacological use. To develop these ginsenosides, many kinds of microbes isolated from soils or intestinal microflora have been used (Table 2) [129,130].

However, most of these biotransformed ginseng extracts are inedible, and most of these microbes may not be safe. Therefore, to develop fermented ginseng extract, we must consider fermented bacteria (Are these bacteria edible?) and safe metabolites (Are these metabolites produced by industrial applied microbes similar to metabolites produced by human intestinal microflora?). Nevertheless, these metabolites are good candidates for new drugs.

CONCLUSION

Korean ginseng, American ginseng, and Notoginseng contain saponins, which are found to be dammarane-type, ocotillol-type and oleanane-type oligoglycosides, and polysaccharides. Of these constituents, dammarane ginsenosides can be metabolized into compound K, ginsenoside Rh_1, and protopanaxatriol by intestinal microflora. These metabolites, such as compound K and protopanaxatriol, are pharmacologically active and easily absorbed from the gastrointestinal tract. However, the activities that metabolize these constituents into bioactive compounds differ significantly among individuals. To overcome this challenge, ginsengs have been fermented with enzymes or microbes to produce such metabolites. However, before using these enzymes and probiotics, the safety of these microbes and metabolites must be assessed. The safe ginseng bioproducts produced by enzymes or microbes are valuable for the development of new drugs and/or functional foods.

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