

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

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The major commercial ginsengs are *Panax ginseng* Meyer (Korean ginseng), *P. quinquefolium* 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 Rg₃, Rg₅, and Rk₁ by steaming and heating and are metabolized into metabolites such as compound K, ginsenoside Rh₁, 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 quinquefolium*, *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. quinquefolium* 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. quinquefolium*. 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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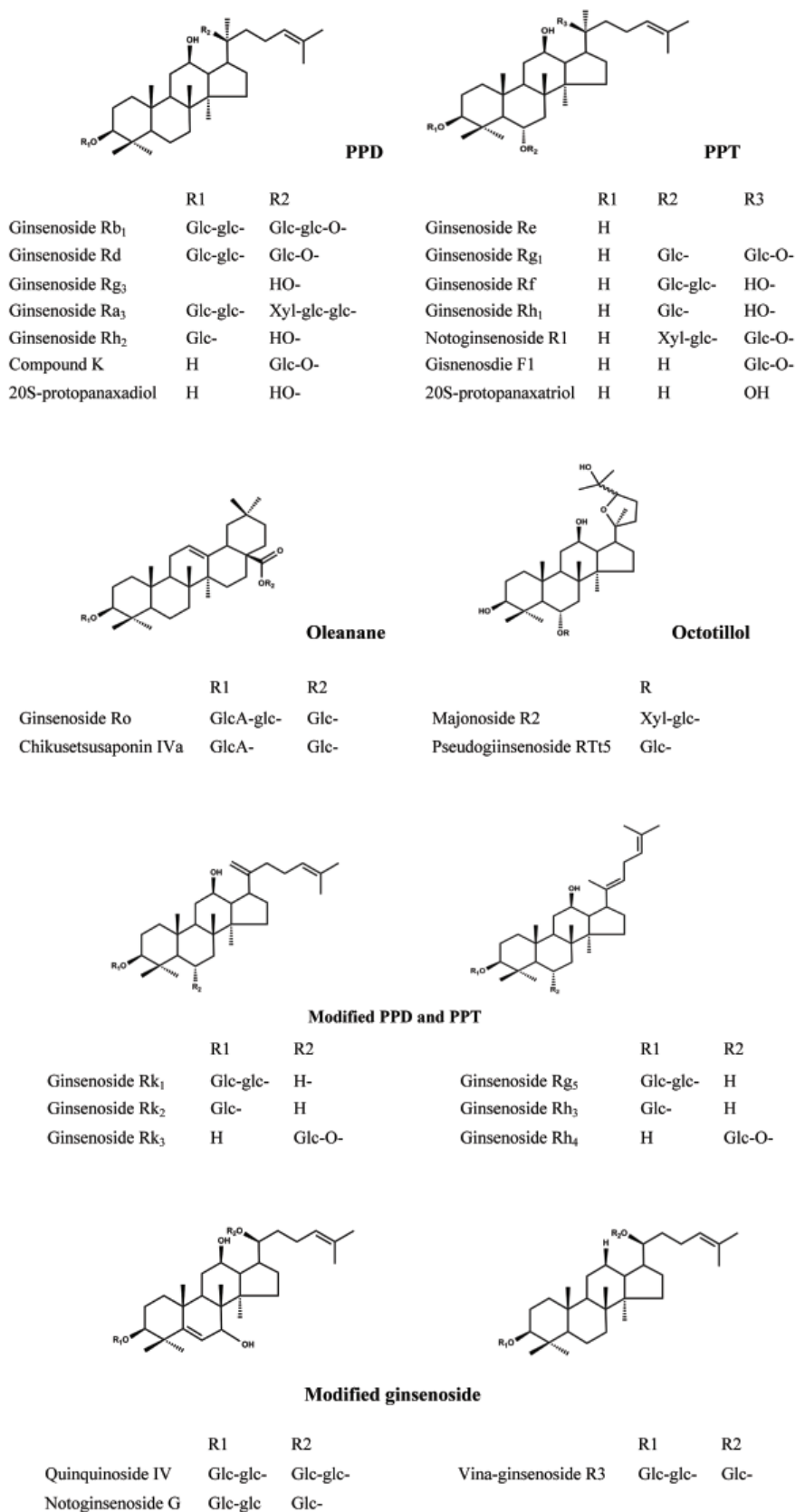


Fig. 1. The structures of representative ginseng saponins. PPD, protopanaxadiol; PPT, protopanaxatriol.

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 Rg₁/Rb₁ 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 Rg₁, which were extracted from the dried root of ginseng [8,9,13]. Kitagawa *et al.* [14] and Kitagawa *et al.* [15] isolated malonyl ginsenosides Rb₁, Rb₂, Rc, and Rd from the dried root of ginseng. Subsequently, the ginsenosides Ro, Ra₁, Ra₂, Ra₃, Re, Rf, Rg₁, Rg₂, Rg₃, Rh₁, the notoginsenosides R4, 20-gluco-ginsenoside Rf, koryoginsenoside R1, and R2, and the ginsenosides Rb₁, Rb₂, Rc, and Rd, have been reported [11,16].

Recently, Ruan *et al.* [17] isolated the malonylginsenoside Ra₃ from the root of *P. ginseng*. Zhu *et al.* [18] isolated 6 new protopanaxatriol-type ginsenosides, the ginsenosides Re₁, Re₂, Re₃, Re₄, Re₅, Re₆, and 10 known protopanaxatriol ginsenosides, including the ginsenoside Rg₁ 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. notoginseng*)

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 Ra₁, Ra₂, and Ra₃, and the notoginsenoside R4 from the steamed root of ginseng (red ginseng). Kasai *et al.* [20] isolated the ginsenosides Ra₁, Ra₂, Ra₃, Rs₁, and Rs₂, the notoginsenoside R1, and the quinquenoside R1. Thereafter, the ginsenosides Ro, Rb₁, Rb₂, Tc, Rd, Re, Rf, Rg₁, Rg₂, Rg₃, Rh₁, the ginsenosides Rh₂, 20R-ginsenoside Rh₁, 20S-ginsenoside Rg₃, and 20R-ginsenoside Rg₂ were isolated from red ginseng. Ryu *et al.* [21] isolated the ginsenoside Rg₆ and 20(E)-ginsenoside F4 from red ginseng. Baek *et al.* [22] isolated the ginsenoside Rh₄. Then, the ginsenosides Rs₁, Rs₂, Rs₃, and Rs₄, the quinoginsenoside R4, the ginsenosides Rg₃, Rg₅, Rg₆, F4, and Rf₂ were isolated from red ginseng [23,24]. In particular, large quantities of the ginsenosides Rh₁, Rg₃ and Rg₂ were found in red ginseng. Under intense steaming or heating, ginsenoside Rg₃ may be further transformed to 20S-Rh₂ and 20R-Rh₂, and these ginsenosides subsequently become aglycone 20S-protopanaxadiol, 20R-protopanaxadiol, or even 20-dehydroprotopanaxadiol through chemical degradation. Ginsenosides Rk₁ and Rg₅ are again transformed into the degradation products Rk₂ and Rh₃. Rh₁ can be changed into the aglycones 20S-protopanaxatriol, 20R-protopanaxatriol, and 20-dehydroprotopanaxatriol.

Shoji *et al.* [25] and Shoji *et al.* [26] were interested in the constituents of the leaves of *P. ginseng*. They isolated the ginsenosides Rb₁, Rb₂, Rc, Rd, Re, Rg₁, F1, F2, and F4 from the leaves and stems. The ginsenosides F4, 20R-protopanaxadiol, 20R-protopanaxatriol, ginsenoside Rh₃, 20R-ginsenoside Rh₂, 20S-ginsenoside Rh₂, ginsenosides Rh₁, Rg₃, Rg₂, Rg₁, Re, Rd, Rc, Rb₂, and Rb₁ were isolated from the flower buds of *P. ginseng* [27]. Ginsenosides Rh₅, Rh₆, Rh₇, Rh₈, Rh₉ and Rg₇, 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-3 β ,6 α ,12b-,20-tetrahydroxydammarane-25-ene-24-one 20-O- β -glucopyranoside, 20S-3 β ,6 α ,12 β -,20,24,25-pentahydroxydammarane 20-O- β -D-glucopyranoside, 20S,23E-3 β ,6 α ,12b,20,25-tetrahydroxydammarane-23-ene 20-O- β -glucopyranoside and six known compounds from the leaves of *P. ginseng*. Wu *et al.* [32] isolated 3 β ,6 α ,12 β -triol-22,23,23,25,26,27-hexanordammarane-20-one and dammar-20(22),24-diene-3 β ,6 α ,12 β -triol from the leaves of *P. ginseng*. Huang *et al.* [33] isolated new 20R,22(xi),24(S)-dammar-25(26)-ene-3 β ,6 α ,12 β ,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

Rb₁, Rb₂, Rc, Rd, Re, Rg₁, F3, and M7cd from the flower buds of *P. ginseng*. They also isolated ginsenosides Rb₂, Rd, Rd, Re, Rg₂, 20R-protopanaxatriol, 20R-ginsenoside Rh₁, 20R-ginsenoside Rg₂, notoginsenoside-E, and gypenoside XVII from the flower buds of *P. ginseng* [25]. Yoshikawa *et al.* [36] isolated new floral-ginsenosides 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 methoxydammarane-3 β ,6 α ,12 β ,20-triol, 20R-25-methoxydammarane-3 β ,6 α ,12b,20-tetrol, and 20R-20,25 dimethoxydammarane-3 β ,6 α ,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, panaxans 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 immunomodulating 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 \times 10⁴, 1.0 \times 10⁵), 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 sesquiterpene 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 sesquiterpene 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 QUINQUEFOLIUM*

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

Saponins

Saponins, particularly ginsenosides, are constituents of American ginseng (*P. quinquefolium*). More than 60 ginsenosides, including dammarane-, ocotillol-, and oleanane-types, have been isolated from the roots, leaves, stems, flower buds and berries of *P. quinquefolium*. Chen *et al.* [51] isolated quinquenosides L10 and L16 from the leaves and stems of *P. quinquefolium*. Jiang *et al.* [52] isolated two new saponins, 3 β ,12 β ,20S trihydroxydammar-23-ene-3-*O*-{[β -D-glucopyranosyl(1 \rightarrow 2)]- β -D-glucopyranosyl]-20-*O*-[α -L-arabinopyranosyl(1 \rightarrow)]- β -D-glucopyranoside and 3 β -20S-dihydroxy-12 β -23R-epoxydammar-24-ene-3-*O*-{[β -D-glucopyranosyl(1 \rightarrow 2)]- β -D-glucopyranosyl]-20-*O*-[β -D-xylosyl(1 \rightarrow 6)]- β -D-glucopyranoside from the leaves of *P. quinquefolium*. Many ginsenosides have been isolated from *P. quinquefolium*. Protopanaxadiol-type ginsenosides isolated from the roots, leaves and stems, and flower buds of American ginseng are the ginsenosides Rb₁, Rc, Rb₂, Rb₃, Rd, Rg₃, F2, Rs₁, 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 Rg₁, Rg₂, Re, Rg₂, F3, Ia, F1, Rh₁, 20S-acetyl ginsenoside Rg₂, 20R-acetyl ginsenoside Rg₂, floralquinquenoside E, 20R-ginsenoside Rg₂, Rh₁, 20S-protopanaxatriol, and 20R-protopanaxatriol [52,54,56]. Du *et al.* [57] isolated four malonyl-ginsenosides, Rb₁, Rc, Rb₂, 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. quinquefolium* [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 Rg₁, Re, Rb₁, Rc, Rb₂, Rb₃, and Rd, decreased remarkably; however, less polar ginsenosides, including Rg₂, Rg₃, Rg₅, Rh₂, Rk₁, and Rs₄, 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, Rk₁/Rg₅ and Rk₃/Rh₄, 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 Rb₃, ginsenoside Rd, ginsenoside Rs₁, pseudo-ginsenoside-RC1, pseudo-ginsenoside-F8, quinquenoside III, ginsenoside I, notoginsenoside-E, ginsenoside Re, ginsenoside Rg₁, ginsenoside Rg₂, ginsenoside-F3, ginsenoside Ia, quinquenoside L9, pseudo-ginsenoside RT5, pseudo-ginsenoside F11, and 24(S)-pseudo-ginsenoside F11 from the flower buds of *P. quinquefolium* L. Qiu *et al.* [62] isolated a new saponin quinquefoloside-L(c) (3 β ,12 β ,20Strihydroxy-25-methoxy-25-methoxydammar-23-ene-3-*O*- β -D-glucopyranosyl(1 \rightarrow 2)]- β -D-glucopyranosyl-20-*O*- β -xylopyranosyl(1 \rightarrow 6)]- β -D-glucopyranoside) from the leaves of *P. quinquefolium*. 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. quinquefolium* [63]. These glycans are poly furanosyl-pyranosylsaccharides. Hypoglycemic glycans, such as quinquefolans A, B, and C, were isolated from the roots of *P. quinquefolium* [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. quinquefolium* [65-67]. Nakamura *et al.* [54] isolated three flavonoids and 3 flavonoid glycosides, kaempferol 3-*O*- β -D-sophoroside-7-*O*- α -L-rhamnopyranoside, 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. quinquefolium* [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 Rb₁, Rb₂, 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 Rb₁, 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-3 β ,12 β ,26-triol, and 20R-dammaran-3 β ,12 β ,20,25-tetrol) by acidic hydrolysis [76]. Cui *et al.* [76] isolated two new ginsenosides, notoginsenoside Rw1 [6-*O*- β -D-xylopyranosyl-20-*O*- β -D-xylopyranosyl-(1 \rightarrow 6)- β -D-glucopyranosyl-dammar-24-ene-3b,6a,12b,20(S)tetraol] and Rw2 [6-*O*- β -Dxylopyranosyl-(1 \rightarrow 2)- β -D-glucopyranosyl-dammar-22-ene-(trans)-3 β ,6 α ,12 β ,20(S),25-pentaol], from the roots of *P. notoginseng*. Wan *et al.* [77] isolated 5,6-didehydroginsenoside Rd, 5,6-didehydroginsenoside Rb₁ 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-3 β ,12 β ,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 11 notoginsenosides-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 Rg₁, Re, Rb₁, Rd and notoginsenoside R1 from Notoginseng. As seen on the steaming process of red ginseng, steaming notoginseng increased the contents of ginsenosides Rh₁, Rg₂, Rg₃, Rh₂, and 20R-ginsenoside Rg₂. 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 Rg₅, Rg₂, Rg₁, Re, Rh₄, Rd, 20R-ginsenoside Rg₃, ginsenoside Rg₃, 20R-ginsenoside Rh₁, ginsenoside Rh₁, the notoginsenosides E, R2, and R1, the gypenoside XVII, 20R-25-hydroxyginsenoside Rh₁, and 20S-25-hydroxyginsenoside Rh₁.

Polysaccharides

Sanchinan-A (1.5 \times 10⁶), 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-O-sophoroside, 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 Rh₁ and F1 were detected in the blood [90,91]. Ginsenosides Rb₁ and Rb₂ were not detected. When ginsenoside Rb₁, 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 Rb₁ was not detected. Furthermore, compound K was detected in the blood and intestinal contents when ginsenoside Rb₁ was orally administered to gnotobiotic rats [94]. However, when ginsenoside Rb₁ was orally administered to germ-free rats, compound K and ginsenoside Rb₁ were not detected in the blood and intestinal contents. When Notoginseng extract, whose main constituents are ginsenoside Ra₃, Rb₁, Rd, Re, and Rg₁ and notoginsenoside R1, was orally administered to rats, the compounds that were mainly absorbed into the blood were ginsenoside Ra₂, Rb₁, and Rd and compound K [95]. These results are not consistent. Nevertheless, compound K, a metabolites of protopanaxadiol ginsenosides, always are absorbed into the blood. Furthermore, of parental ginsenosides and their metabolites, compound K, ginsenoside Rh₁, Rh₂, and protopanaxatriol showed the most potent biological effects compared with those of parental compounds. For example, compound K and 20(S)-ginsenoside Rh₂ exhibited the most potent cytotoxicity against tumor cells [96,97]. Ginsenoside Rb₁ and Rb₂ 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 Rg₁ were easily transformed to ginsenoside Rh₁ 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 Rh₂

Ginsenoside Rh₂ showed anti-tumor [99], anti-inflammatory [108], anti-pruritic [109], antiallergic [106], hepatoprotective [110], hypoglycemic, and hypolipidemic effects in mice [111,102]. Ginsenoside Rh₂ effectively inhibited adipocyte differentiation via PPAR- γ inhibition [112] and improved insulin sensitivity [113]. Ginsenoside Rh₂ ameliorated transient focal ischemia in rats [114].

Ginsenoside Rh₁

Ginsenoside Rh₁ exhibited anti-inflammatory [115], antiallergic [106], anti-dermatitic [116] effects *in vitro* and *in vivo*. Ginsenoside Rh₁ 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 PPAR γ 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	<i>Bifidobacterium longum H-1</i>	β -D-Glucosidase/ α -L-Arabinosidase	[131]
Ginseng extract		<i>Sulfolobus solfataricus</i>	β -D-Glycosidase (recombinant: 83)	[132]
Ginseng extract		<i>Aspergillus niger</i>	Pectinase (commercial)	[133]
Ginseng extract	Rh ₂	<i>Bifidobacterium longum H-1</i>	β -D-Glucosidase (crude)	[134]
Ginseng extract	Rg ₃	<i>Trichoderma reesie</i>	Cellulase (commercial)	[135]
Ra ₁ , Ra ₂	Rb ₂ , Rc	<i>Bifidobacterium breve</i>	β -D-Xylosidase (purified)	[136]
Gypenoside-5	Rd	<i>Absidia</i> sp.	α -L-Rhamnosidase (purified)	[137]
Rb ₂		<i>Bifidobacterium breve</i>	α -L-Arabinopyranosidase (purified)	[138]
Rc		<i>Bifidobacterium breve</i>	α -L -Arabinopyranosidase (purified)	[136]
Rb ₁		<i>Chloroflexus aurantiacus</i>	β -D-Glucosidase (recombinant)	[139]
Rb ₁		<i>Cladosporium fulvum</i>	β -D-Glucosidase (purified)	[140]
Rb ₁ , Rb ₂ , Rc		<i>Thermus caldophilus</i>	β -D-Glycosidase (recombinant)	[141]
PPD mixture		<i>Trichoderma viride</i>	Cellulase (commercial)	[142]
Rb ₁ , Rb ₂ , Rc	Rg ₃	<i>Penicillium</i> sp.	Lactase (commercial)	[143]
Rb ₁ , Rd		<i>Paecilomyces bainier</i>	β -D-Glucosidase (purified)	[144]
Rb ₁ , Rb ₂ , Rc	F ₂	<i>Aspergillus oryzae</i>	Lactase (commercial)	[142]
Rb ₁ , Rb ₂ , Rc		<i>Penicillium</i> sp.	Lactase (commercial)	[143]
Rb ₁ , Rb, Rc	C-K, C-Y, C-Mc	<i>Sulfolobus acidocaldarius</i>	β -D-Glycosidase (recombinant)	[132]
Rb ₁ , Rb, Rc,		<i>Paecilomyces bainier</i>	β -D-Glucosidase (purified)	[145]
Rb ₁	C-K	<i>Fusobacterium</i> sp.	β -D-Glucosidase (purified)	[146]
Rb ₁ , Rb ₂ , Rc		<i>Aspergillus oryzae</i>	β -D-Galactosidase (commercial)	[142]
Rb ₁ , Rb ₂ , Rc		<i>Penicillium</i> sp.	Lactase (commercial)	[143]
Rb ₁ , Rb ₂ , Rb ₃ , Rc		<i>Aspergillus</i> sp.	β -D-Glycosidase (purified)	[147]
Rg ₃	Rh ₂	<i>Fusarium proliferatum</i>	β -D-Glucosidase (purified)	[148]
Re	Rg ₁	<i>Penicillium</i> sp.	Hesperidinase (commercial)	[143]
Re		<i>Bacterodites</i> sp.	α -D-Rhamnosidase (purified)	[149]
Re	Rg ₂	<i>Aspergillus oryzae</i>	β -Galactosidase (commercial)	[142]
Re		<i>Bacterodites</i> sp.	β -D-Glucosidase (purified)	[150]
Rg ₁	F ₁	<i>Bacterodites</i> sp.	β -D-Glucosidase (purified)	[150]
Re, Rg ₁		<i>Penicillium decumbens</i>	Naringinase (commercial)	[142]
Rg ₁	Rh ₁	<i>Bacterodites</i> sp.	β -D-Glucosidase (purified)	[150]
Rg ₂		<i>Aspergillus oryzae</i>	β -Galactosidase (commercial)	[143]
Rg ₂		<i>Absidia</i> sp.	α -L -Rhamnosidase (purified)	[151]
Rg ₁ , Rg ₂ , Rf		<i>Penicillium</i> sp.	Lactase (commercial)	[143]
Rf		<i>Aspergillus niger</i>	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]. Antitroviral 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, Rh₁, Rh₂, Rk₁, Rh₃, Rh₄, 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 Rh₁, 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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