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Review article

Gut microbiota-mediated pharmacokinetics of ginseng saponins

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ABSTRACT

Orally administered ginsengs come in contact with the gut microbiota, and their hydrophilic constituents, such as ginsenosides, are metabolized to hydrophobic compounds by gastric juice and gut microbiota: protopanxadiol-type ginsenosides are mainly transformed into compound K and ginsenoside Rh2; protopanaxatriol-type ginsenosides to ginsenoside Rh1 and protopanaxatriol, and ocotillol-type ginsenosides to ocotillol. Although this metabolizing activity varies between individuals, the metabolism of ginsenosides to compound K by gut microbiota in individuals treated with ginseng is proportional to the area under the blood concentration curve for compound K in their blood samples. These metabolites such as compound K exhibit potent pharmacological effects, such as antitumor, anti-inflammatory, antidiabetic, antiallergic, and neuroprotective effects compared with the parent ginsenosides, such as Rb1, Rb2, and Re. Therefore, to monitor the potent pharmacological effects of ginseng, a novel probiotic fermentation technology has been developed to produce absorbable and bioactive metabolites. Based on these findings, it is concluded that gut microbiota play an important role in the pharmacological action of orally administered ginseng, and probiotics that can replace gut microbiota can be used in the development of beneficial and bioactive ginsengs.

1. Introduction

Most herbal medicines are orally administered to humans, and the components inevitably come into contact with the gut microbiota in the gastrointestinal tract where trillions of microbes reside. The gut microbiota exhibits diverse physiological activities including the ability to metabolize orally administered and bile-secreted xenobiotics (e.g., drugs, phytochemicals) [1–3]. Gut microbiota transforms the constituents of orally administered hydrophilic drugs and phytochemicals before absorption by gastrointestinal tract into the blood. Studies on the metabolism of phytochemicals found in natural products, such as ginseng, by the gut microbiota are important in understanding their biological effects [4,5].

This review describes gut microbiota-mediated metabolism of ginsenosides such as protopanaxadiol- type, protopanaxatriol-type, oleanane-type, and ocotillol-type ginsenosides and their bioactive metabolites.

2. Gut microbiota

The neonate is born in a germ-free state. Immediately after birth, they are exposed to microbes present within the parturient canal, on the skin of mothers and nurses, and in ambient air. These microbes colonize on body surfaces and the gastrointestinal and vaginal tracts [6,7]. Newer molecular methods have revealed that the gastrointestinal tract hosts over 2,000 species of microbiota in humans. Most species belong to eight dominant phyla: *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria, Fusobacteria*, *Cyanobacteria*, and *Verrucomicrobia* [8,9]. More than 80% of these microbes belong to the phyla *Firmicutes* and *Bacteroides*; *Firmicutes* includes *Clostridia* and *Bacilli*; and *Bacteroidetes* includes *Bacteroides* spp. The highly complex gut ecosystem varies between individuals due to factors, such as diet, genetics, hormones, and drugs [10]. It exhibits various physiological actions: fermentation of carbohydrates and proteins that are not digested in the upper gut, production of vitamins B and K, protection against pathogens,

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stimulation of innate and adaptive immune responses, and metabolism of orally administered hydrophilic phytochemicals and drugs.

3. Ginseng constituents

Ginseng refers to the dried roots of the species *Panax* sp. (Family Araliaceae), including *Panax ginseng* Meyer (Korean ginseng or Asian Ginseng), which has been used as a herbal medicine for more than 2000 years [11], *Panax quinquefolius* L. (American Ginseng), *Panax notoginseng* (Burk.) FH Chen (Notoginseng), and *Panax vietnamensis* Ha et Grushv. (Vietnamese Ginseng) [12–14]. *P. ginseng* is the most commonly used. Garriques prepared the saponin fraction of *P. quinquefolius* [1]. Its constituents were not identified until 1963 [15]. Shibata et al. [16–18] isolated saponins from the root of *P. ginseng* in 1963 and identified their structures. Since then, many researchers have isolated the constituents including ginsenosides. Approximately 200 substances, such as ginsenosides, polysaccharides, and polyacetylenes have been isolated from Korean ginseng [19,20] and more than 100 from American ginseng, notoginseng, and Vietnamese ginseng [12–14].

Shibata et al. [16–18,21] established the chemical structures of main prosapogenins 20S-protopanaxadiol, 20S-protopanaxatriol, prosapogenin, and ginsenoside Rg1 found in the dried root of *P. ginseng*. Kitagawa et al. [22,23] isolated malonyl ginsenoside Rb1, Rb2, Rc, and Rd; Ruan et al. [24] isolated malonyl ginsenoside Ra3; Zhu et al. [25] isolated six protopanaxatriol-type ginsenosides Re1, Re2, Re3, Re4, Re5, and Re6 and 10 known protopanaxatriol ginsenosides including ginsenoside Rg1.

From red ginseng (steamed *P. ginseng*), Matsumura et al. [26] isolated ginsenosides Ra1, Ra2, and Ra3 and notoginsenoside R4. Kasai et al. [27] isolated ginsenosides Ra1, Ra2, Ra3, Rs1, and Rs2, notoginsenoside R1, and quinquenoside R1. Thereafter, ginsenosides Ro, Rb1, Rb2, Tc, Rd, Re, Rf, Rg1, Rg2, Rg3, Rh1, Rh2, 20R-ginsenoside Rh1, 20S-ginsenoside Rg3, and 20R-ginsenoside Rg2 were also isolated by [27]. Ryu et al. [28] isolated ginsenoside Rg6 and 20(E)-ginsenoside F4. Baek et al. [29–31] isolated ginsenoside Rh4 [29] as well as ginsenoside Rs1, Rs2, Rs3, and Rs4, quinoginsenoside R4; ginsenoside Rg3, Rg5, Rg6, F4, and Rf2 [30,31]. Ginsenosides Rh1, Rg3, and Rg2 were found in large quantities. Under intense steaming or heating, ginsenoside Rg3 can transform into 20S-Rh2 and 20R-Rh2 and subsequently form the aglycone 20S-protopanaxadiol and 20R-protopanaxadiol or even 20-dehydroprotopanaxadiol through chemical degradation [32–34]. Ginsenoside Rk1 and Rg5 can transform into their degradation products, such as Rk2 and Rh3, and Rh1 into aglycone 20S-protopanaxatriol and 20R-protopanaxatriol or even 20-dehydropropanaxatriol.

In American ginseng (*P. quinquefolius*), > 60 ginsenosides, including dammarane, ocotillol, and oleanane types, have been isolated: ginsenoside Rb1, Rd, and Re as main constituents, including ocotillol-type ginsenosides (24R-pseudoginsenoside F11, pseudoginsenoside RT5, F-11, 24R-vina-ginsenoside R1) and oleanane-type ginsenosides (ginsenoside Ro, chikusetsusaponin Iva) [4].

In *P. notoginseng*, a total of 56 dammarane-type saponins have been isolated: protopanaxadiol-type and protopanaxatriol ginsenosides, such as ginsenosides Ra3,RK3, Rh4, Rg3, Rk1, Rg5, F2, Rh1, Rg1, Re, Rd, Rb1, and Rb2, 6′-O-acetylginsenoside Rh1, and another group of saponins, notoginsenosides A – N, R1 – R4, R6 – R9, Fa, Fc, and Fe and gypenoside X VII [14,35–39].

From *P. vietnamensis*, Nguyen et al. [14,40,41] isolated ginsenoside Rh1, Rg1, Re, Rd, Rb3, Rb2, and Rb1; pseudoginsenoside RS1; notoginsenosidesR1 and Fa; oleanolic acid; and ocotillol-type saponins (pseudoginsenoside-RT4, 24(S)-pseudoginsenoside F11, majonoside F1, R1, and R2); vinaginsenoside R3, R4, R5, R6, R7, R8, and R9; 20-glucoginsenoside Rf; ginsenoside Rc; notoginsenoside R6; quinquenoside R1; and gypenoside XVII. In addition, Duc et al. [42] isolated 6-O-β-D-glucopyranosyl 20(S),25-epoxydammarane-3β,6α,12β,24α-tetrol, 6-O-β-D-xylopyranosyl-(1–>2)-β-D-glucopyranosyl 20(S),25-epoxydammarane-3β,6α,12β,24α-tetrol; 6-O-β-D-glucopyranosyl dammarane-3β,6α,12β,20(S),24 xi,25-hexol; 3-O-[β-D-glucopyranosyl-(1–>2)-β-D-glucopyranosyl]-20-O-β-D-glucopyranosyl dammarane-3β,12 β,20(S),24 xi,25-pentol; and 6-O-β-D-xylopyranosyl-(1–>2)-β-D-glucopyranosyl 20(S),24(S)-epoxydammarane-3β,6α,12β,25 xi,26-pentol [42].

4. Absorption, distribution, metabolism, and excretion of ginseng phytochemicals

The pharmacological effects of ginsengs, particularly their saponins including ginsenosides, may be dependent on their absorption, distribution, metabolism, and excretion (ADME), similar to drugs (Fig. 1). In a pharmacokinetic study, Tawab et al. [43] investigated the parent ginsenosides and their metabolites in the plasma and urine samples of two individuals orally treated with Ginsana extract (ginseng saponin fraction, Pharmaton S.A., Lugano, Switzerland) by liquid chromatography–mass spectrometry/mass spectrometry. The metabolites ginsenosides Rh1, F1, and compound K were detected in the plasma and urine. However, the metabolites were not detected in Ginsana extract. Therefore, these metabolites (hydrolysates) may be produced for parental ginsenosides by gut microbiota or by the liver. Although ginsenoside Rb1 was detected in the plasma and urine of one individual, it was detected at the lower limit of detection. Akao et al. [44,45] conducted a pharmacokinetic study of compound K in germ-free and gnotobiotic rats. They could not detect ginsenoside Rb1 in both rats, but they detected compound K in gnotobiotic rats, not in the germ-free rats. In individuals orally administered ginseng extract, Shibata et al. [46] did not detect ginsenoside Rb1, but detected compound K. In our previous studies, we detected compound K in rats orally treated with 0.2 g/kg ginseng extract. Maximum concentration, time to maximum concentration, and area under the curve (AUC) were 24.1 ± 5.5 ng/mL, 15.2 ± 1.8 h, and 153.1 ± 30.6 ng·h/mL, respectively [47–49]. We found that the absorption of compound K was affected by diets including prebiotic fiber (nutriose). We also performed a pharmacokinetic study of compound K in individuals (n = 34) orally treated with ginseng powder [1,49]. Maximum concentration, time to maximum concentration, and AUC were found to be 27.89 ± 24.46 ng/mL, 10.76 ± 2.07 h, and 221.98 ± 221.42 ng h/mL, respectively. These findings suggest that compound K may be the main metabolite produced by intestinal bacteria in humans orally administered ginseng.

5. Metabolism of protopanaxadiol-type and protopanaxatriol-type ginsenosides in gastrointestinal tract by gastrointestinal juice and gut microbiota

To understand the metabolism of ginsenosides in the gastrointestinal tract, many experiments were conducted *in vitro* and *in vivo* [44,50–53]. Karikura et al. [33] and Han et al. [51] reported that protopanaxadiol-type ginsenosides Rb1 and Rb2 transformed into ginsenoside Rg3 in diluted hydrochloric acid *in vitro*. In addition, ginsenoside Rb1 transformed into a 25-hydroperoxy-23-ene derivative. Ginsenoside Rb2 transformed into 25-hydroxyl-23-ene, 24-hydroxy-25-ene, 25-hydroperoxy-23-ene, and 24-hydroperoxy-25-ene derivatives. Thus, protopanaxadiol-type ginsenosides hydrolyzed the C-20 glycosyl moiety and hydrated or oxygenated the side chain. Nevertheless, the amount of their metabolites in rat stomach was negligible.

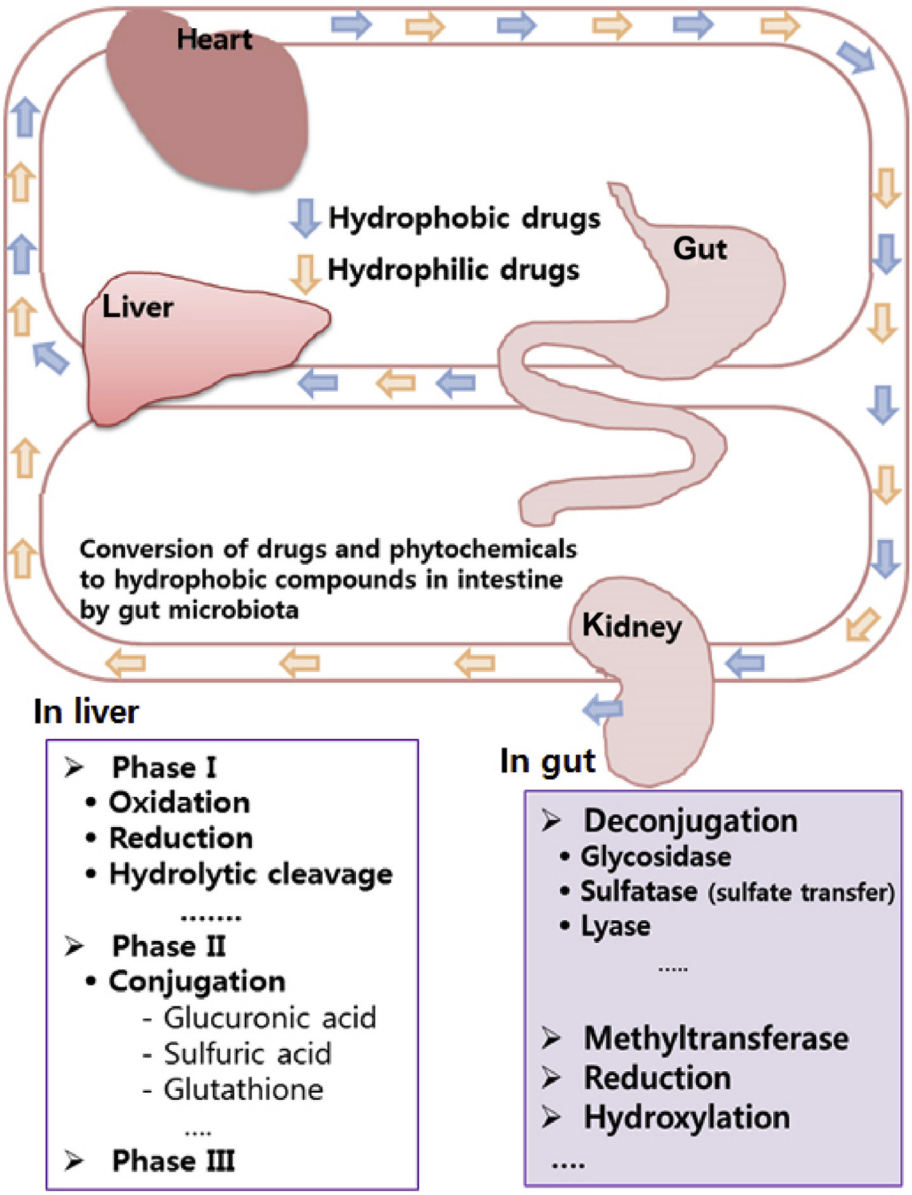

Fig. 1. Fates of orally administered drugs and phytochemicals in humans and animals. Orally administered drugs and phytochemicals in humans and animals are converted to hydrophobic compounds in the intestine by enzymes of gut microbiota such as β-D-glucosidase, and delivered into the liver, which metabolizes these hydrophobic metabolites to hydrophilic compounds by enzymes of phase I–III, such as uridine 5′-diphospho-glucuronosyltransferase.

After our incubation in a diluted condition at 60°C or at boiling temperature, protopanaxadiol-type ginsenosides Rb1, Rb2, and Rc transformed into ginsenoside Rg3, Rg5, and Rk1; however, the transformation was negligible at 37°C [32]. These findings suggest that orally administered protopanaxadiol-type ginsenosides may be resistant to the gastric juice, but can be transformed by heat under acidic condition.

Hydrophilic ginsenosides, when orally ingested by humans and animals, come into contact with gut microbiota in the gastrointestinal tract and can be metabolized to hydrophobic metabolites by the gut microbiota [4,5]. Hydrophobic metabolites are easily absorbed from the gastrointestinal tract into the blood compared with the parent ginsenosides. When ginseng was orally administered in humans, compound K (a hydrophobic metabolite of ginsenosides) was detected in the blood as the main component [43,46]; a small quantity of ginsenoside Rb1, but not ginsenoside Rb2, Rc, and Re, was detected in the blood of one of two individuals. Akao et al. [44,45] and Park et al. [54] also found compound K in the intestinal content, blood, and urine of conventional and gnotobiotic rats orally treated with ginsenoside Rb1. Moreover, Kato et al. [55] detected compound K in the blood of human following the intake of red ginseng powder. Although ginsenosides Rb1, Rb2, Rc, and Re were detected in some studies [43–45], the levels were insufficient to exhibit show a biological effect.

Protopanaxatriol-type ginsenosides Rg1 and Re are more labile to acidic condition than protopanaxadiol-type ginsenosides. Protopanaxatriol-type ginsenosides are transformed into ginsenosides Rh1 and Rg2 under acidic condition. The metabolite ginsenoside Rh1 was absorbed from the stomach and small intestine. However, ginsenoside Rg2 was not detected in the blood because the rhamnosyl moiety could not be absorbed due to the absence of rhamnose sugar transporter, such as quercetin-4-O-

rhamnoglucoside [56]. Ginsenosides Rg1, Rg2, and Re may be metabolized to ginsenoside Rh1 and protopanaxatriol by the gut microbiota. These metabolites are easily absorbed into the blood. These findings suggest that protopanaxatriol-type ginsenosides can be hydrolyzed in the stomach by gastric juice and the metabolites can be absorbed from stomach and small intestine. However, most protopanaxatriol-type ginsenosides are metabolized by the gut microbiota and the metabolites are absorbed from the lower part of the intestine.

Of the gut microbiota, many bacteria catalyze the metabolic reactions of ginsenosides. Protopanaxadiol-type ginsenoside Rb1, Rb2, and Rc are transformed into the monoglucosylated ginsenoside compound K through the cleavage of the sugar moieties by gut microbiota, which produces β-glucosdiase, β-xylosidase, α-arabinofuranosidase, and/or α-arabinopyranosidase (Fig. 2). These enzymes are produced by *Bifidobacterium* H-1, *Provotella oris*, *Fusobacterium* K-60, *Bacteroides* JY-6, *Eubacterium* A-44, *Bifidobacterium* K-506, and *Bifidobacterium* K-110, and *Fusobacterium* K-60 [31,50,51,57–62]. These bacteria also transform protopanaxadiol-type ginsenoside Rg3 and Rg5 into ginsenosides Rh2 and Rh3 (Fig. 3) [58]. Protopanaxatriol ginsenosides Re and Rg1 are transformed to ginsenoside Rh1 or protopanaxatriol by the gut microbiota producing α-rhamnosidase and β-glucosidase. *Fusobacterium* K-60, *Bacteroides* JY-6, *Eubacterium* A-44, and *Bacterodies* HJ-15 produce these enzymes (Fig. 4) [57,63].

6. Metabolism of ginsenoside Ro, vina-majonoside R2, and majonoside R2 in gastrointestinal tract by gut microbiota

In the fecal suspension of humans and mice, ginsenoside Ro is transformed into oleanolic acid. Furthermore, when it was orally administered to mice and their metabolites were analyzed, oleanolic acid was detected in the small intestine, cecum, and colon.

On incubation of VR2 and MR2 with the fecal suspension of humans and mice, they were rapidly transformed into PRT4 and ocotillol [64,65]. The main metabolite in the fecal suspension was ocotillol, followed by PRT4. Therefore, it was proposed that VR2 and MR2 were metabolized to ocotillol in the intestine by the gut microbiota through PRT4 (Fig. 5). When MR2 was orally administered and its metabolites were analyzed in the intestinal fluid 12 h after the treatment, the dominant metabolite was found to be ocotillol, followed by PRT4.

7. Metabolism of ginsenosides in liver

Little is known about the metabolism of ginsenosides in the liver. Wakabayashi et al. [66] reported that orally administered ginsenoside Rb1 was metabolized to compound K in the intestine by the gut microbiota, absorbed into the blood, and metabolized again to stearyl compound K in the liver. Thus, compound K ginsenoside conjugated with fatty acids, such as stearic acid, in the liver, similar to steroids [67]. Moreover, these ginsenosides were metabolized to their hydroxyl derivatives by liver microsomes. The liver microsomal and cytosolic fractions did not hydrolyze β-glucosyl hydrolytic reactions.

8. Pharmacological effects of ginseng constituents and their metabolites

Of Korean, North American, Chinese, and Vietnamese ginsengs, *Panax ginseng* is the most commonly used and studied; it enhances physical performance, promotes vitality, increases resistance to stress and aging, and possesses immunomodulatory activity [68–71].

Many researchers have isolated ginsenosides as bioactive compounds from ginsengs. Dammarane oligoglycosides were found to be the major saponins; oleanane- and ocotillol-type were also identified [4,42,72]. Malonyl-ginsenoside Rb1, Rb2, Rc, and Rd, and ginsenoside Rb1, Rb2, and Rc belong to protopanaxadiol-type ginsenosides Re, Rf, Rg1, and Rg2 belong to protopanaxatriol-type; ginsenoside Ro belong to oleanane-type; and VR2 and MR2 belong to ocotillol-type.

Ginsenosides exhibit antidiabetic [73,74], antitumor [66,75,76], antiallergic [77,78], and anti-inflammatory activities [79],

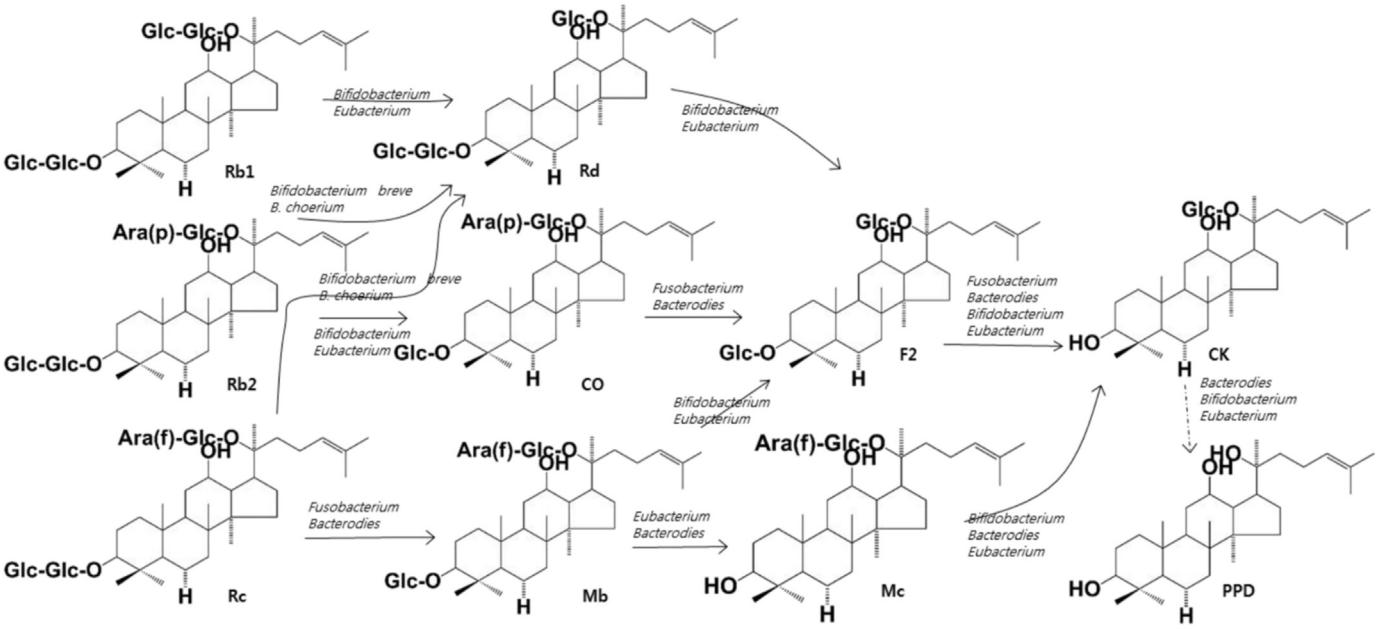

Fig. 2. Proposed metabolism of protopanaxadiol-type ginsenoside Rb1, Rb2, Rc, and Rd isolated from the root of dried ginseng by the gut microbiota. When fresh or dried ginsengs are orally administered in humans or animals, ginsenosides Rb1, Rb2, Rc, and Rd present in these ginsengs are metabolized to compound K or protopanaxadiol through ginsenoside F2 or Mc by gut microbiota.

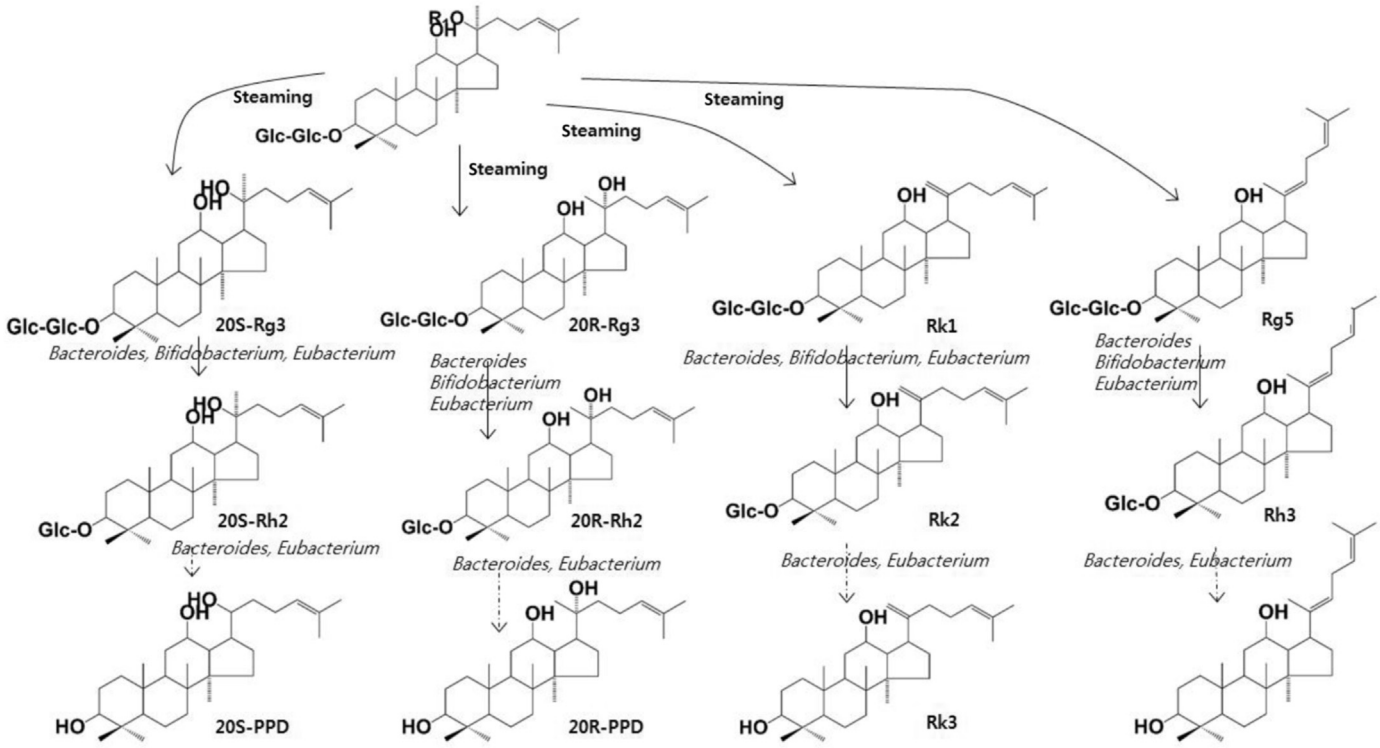

Fig. 3. Proposed metabolism of protopanaxadiol-type ginsenoside Rg3, Rg5, and Rk1 from the root of red ginseng by gut microbiota. Ginsenoside Rb1, Rb2, Rc, and Rd present in fresh and dried ginsengs are transformed into ginsenoside Rg3, Rg5, and Rk1 by heating. When the heat-processed ginsengs, such as red ginseng, are orally treated in humans or animals, the transformed compounds ginsenoside Rg3, Rg5, and Rk1 in these ginsengs are metabolized to ginsenoside Rh2, Rk2, and Rh3 or PPD by gut microbiota.

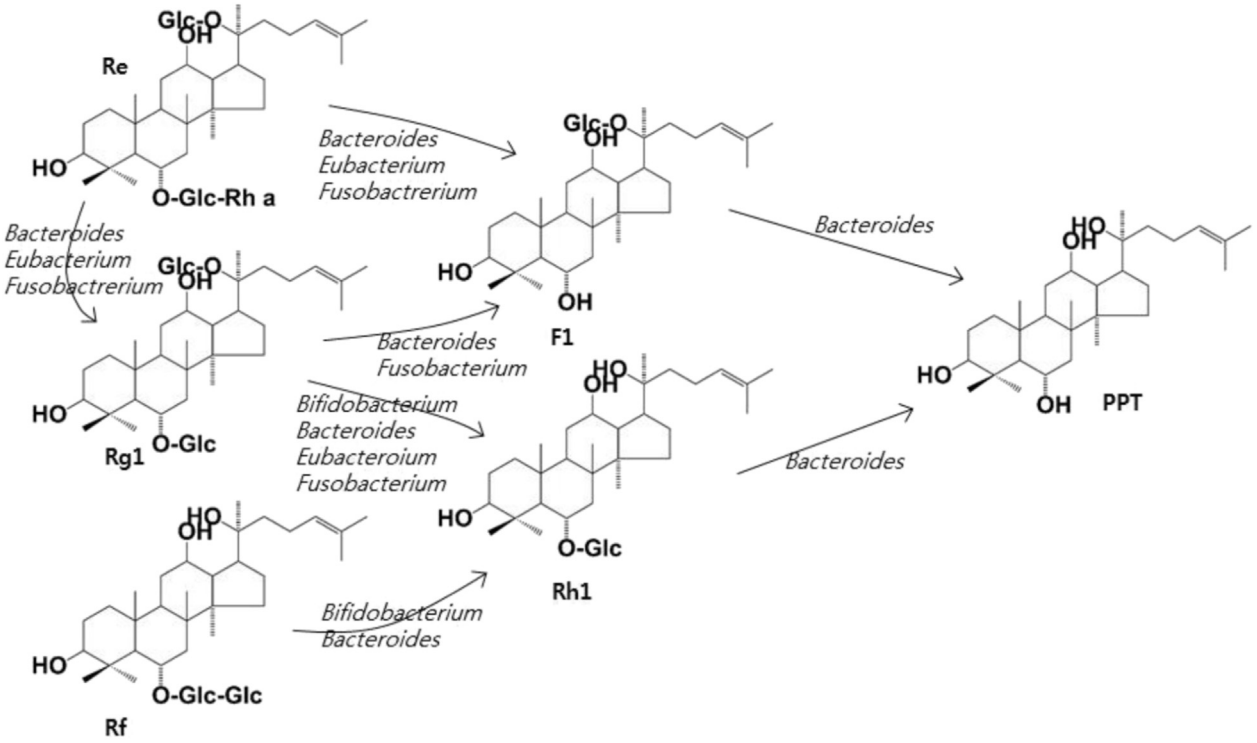

Fig. 4. Proposed metabolism of protopanaxatriol ginsenoside Re, Rg1, and Rf from dried ginseng by gut microbiota. When fresh or dried ginsengs are orally administered in humans or animals, ginsenoside Re, Rg1, and Rf in these ginsengs are metabolized to protopanaxatriol, ginsenoside F1 or ginsenoside Rh1 by gut microbiota.

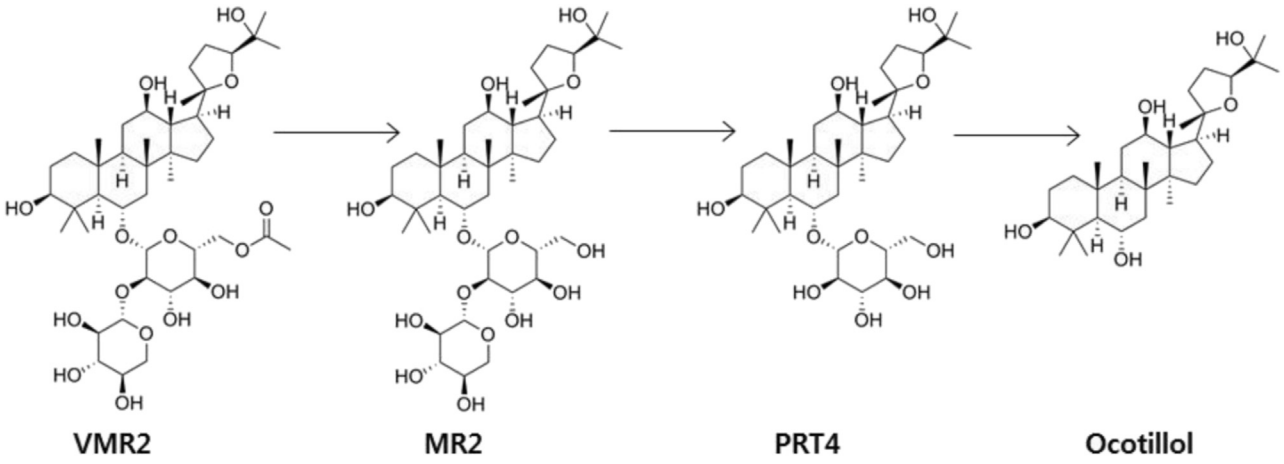

Fig. 5. Proposed metabolism of ocotillol-type vinamajonoside R2 and majonoside R2 from Vietnamese ginseng by gut microbiota. When fresh or dried Vietnamese ginseng (VG) is orally administered in humans or animals, vinamajonoside R2 (VMR2) and majonoside R2 (MR2) present in VG are metabolized to ocotillol through pseudoginsenoside RT4 (PRT4) by gut microbiota.

endothelium-independent aorta relaxation [80], and neuroprotective [81,82], adjuvant-like [83], and immunomodulating effects [84]. However, these pharmacological effects of ginsenosides were observed to be different between *in vitro* and *in vivo* studies. Ginsenosides exhibited an antitumor effect in *in vivo* studies, but contradictively a negligible effect in *in vitro* studies [85,86]. In a recent study, orally administered ginsenosides were metabolized to compound K, ginsenoside Rh2 and Rh1, and protopanaxatriol by the gut microbiota; compound K, ginsenoside Rh2, and protopanaxatriol exhibited potent cytotoxicity against tumor cells [45]. When antiallergic activity of the parent molecules and transformed metabolites were evaluated *in vitro*, ginsenoside Rh1 and Rh2, compound K, and protopanaxatriol were found to show potent inhibitory activity [77,87–89]. These results suggest that the pharmacological effects of ginsengs may be dependent on the metabolism of ginsenosides to bioactive compounds by the gut microbiota.

9. Difference in gut microbiota-mediated ginsenoside-metabolizing enzyme activity between individuals

Gut microbiota transforms ginsenoside Rb1 to compound K *in vitro* and *in vivo* and the compound K is absorbed into the blood [48]. The metabolism of ginsenosides to compound K by intestinal bacteria was proportional to the amount of compound K absorbed into in the blood of volunteers who had been administered ginseng [49]. The compound K-forming activity is significantly different between individuals. Their AUCs are also significantly different. Nevertheless, there was a correlation between the compound K-forming activity and AUC for compound K. Cui et al. [90] determined the total amount of protopanaxatriol and protopanaxadiol in the urine of humans orally administered ginseng preparations. They detected approximately 1.2% of the orally treated dose of protopanaxatriol-type ginsenosides and $< 0.2\%$ of the orally treated dose of protopanaxadiol-type ginsenosides. However, Hasegawa

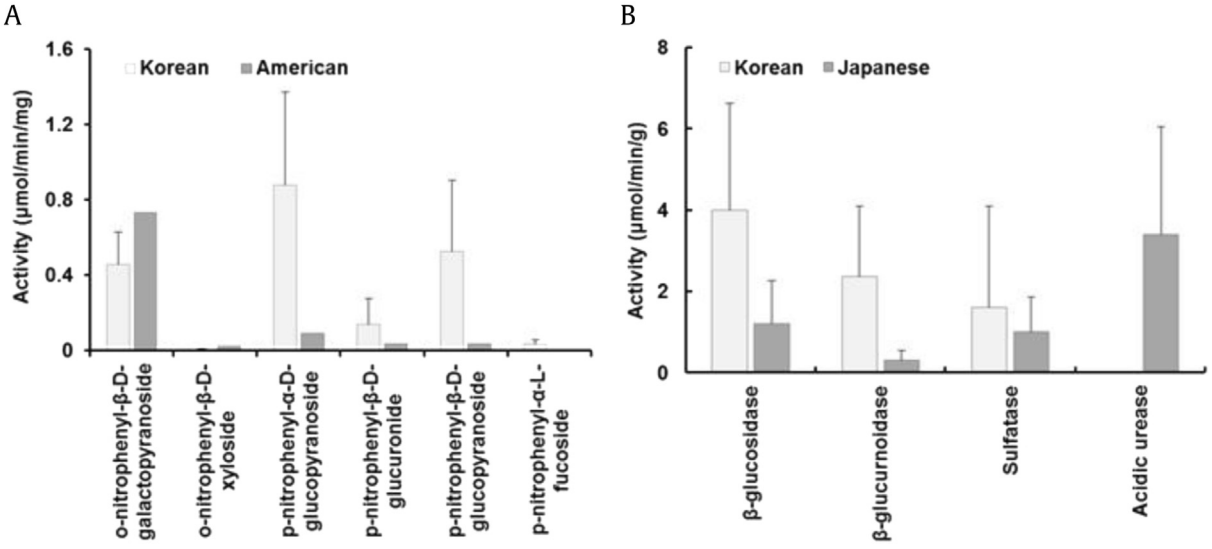

Fig. 6. Difference in β-galactosidase, β-xylosidase, β-glucuronidase, β-glucosidase, and α-fucosidase activities in the fecal suspensions of Korean, American, and Japanese. (A) Difference between Korean and American. The metabolic activity of the Korean fecal suspension was measured according to the method described by Tamura et al. [98]. The data of American was obtained from the study conducted by Tamura et al. [98]. (B) Difference between Korean and Japanese. The metabolic activity of the Korean fecal suspension was measured according to the method described by Kobashi et al. [99]. The data of Japanese were obtained from the study conducted by Kobashi et al. [99].

et al. [67] reported that compound K mono-fatty acid esters such as stearyl compound K, accumulated in mouse liver following intravenous administration. These results suggest that the low absorption of ginsenoside metabolites is dependent on the metabolic activity of gut microbiota and due to the low transforming activity of ginsenosides into hydrophobic metabolites.

10. Fermented/biotransformed ginseng

When medicinal and functional herbs including ginsengs are orally administered to humans, their hydrophilic constituents come in contact with the gut microbiota in the alimentary tract and are transformed into absorbable hydrophobic ginsenosides before absorption from the gastrointestinal tract. All individuals possess characteristic indigenous strains of gut microbiota and the metabolizing activity was found to be significantly different between individuals (Fig. 6) [63,91–99]. Thus, the metabolic activity of gut microbiota was affected by environmental factors such diet, drugs, and genetics. When the metabolism of ginsenosides Rb1 and Rb2 to active compound K was measured, a significant variation was observed between individuals. Therefore, bioactive and absorbable ginsenoside metabolites are valuable in the therapy of diverse diseases. Therefore, to develop bioactive and well-absorbable ginsenoside metabolites containing ginsengs, we developed the fermented ginsengs, which contained bioactive ginsenoside metabolites, such as compound K and ginsenoside Rh1. These metabolites were transformed from ginsenoside Rb1, Rb2, Rc, and Rd by probiotics [31,100]. However, to use these probiotics, their safety and biotransforming activity should be affirmed. Once their safety and efficacy is confirmed, fermentation biotechnology can be valuable in developing novel ginseng preparations. Gut microbiota play an important role in the pharmacological action of ginseng. Therefore, beneficial and bioactive ginsengs can be developed using probiotic fermentation.

11. Conclusion

Hydrophilic components of orally administered ginsengs, such as ginsenosides Rb1 and Rb2, are metabolized to hydrophobic compounds by gastric juice and gut microbiota: the metabolites of protopanxadiol-type ginsenosides are mainly compound K and ginsenoside Rh2 and protopanaxatriol-type ginsenosides are ginsenoside Rh1 and protopanaxatriol. The absorption of the metabolites, such as compound K, is proportional to fecal gut microbiota-metabolizing activity of ginsenosides to compound K. However, the metabolizing activity varies between individuals. Of these metabolites, absorbable and hydrophobic ones, such as compound K, exhibit potent pharmacological effects, such as antitumor, anti-inflammatory, antidiabetic, antiallergic, and neuroprotective effects, than parent ginsenosides, such as ginsenoside Rb1, Rb2, and Re. These findings suggest that the gut microbiota play an important role in the pharmacological action of orally administered ginseng. Furthermore, some probiotics isolated from human gut microbiota transform hydrophilic ginsenosides to hydrophobic and bioactive ginsenosides, such as compound K, and a novel probiotic fermentation technology has been developed to produce absorbable and bioactive metabolites instead of gut microbiota. These findings suggest that the gut microbiota play an important role in the pharmacological action of orally administered ginseng and probiotics that can replace gut microbiota can be used in the development of beneficial and bioactive ginsengs.

Conflicts of interest

The authors have no conflicts of interest.

Acknowledgments

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