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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.

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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.

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