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Review Article

Metabolism and drug interactions of Korean ginseng based on the pharmacokinetic properties of ginsenosides: Current status and future perspectives

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ABSTRACT

Orally administered ginsenosides, the major active components of ginseng, have been shown to be biotransformed into a number of metabolites by gastric juice, digestive and bacterial enzymes in the gastrointestinal tract and also in the liver. Attention is brought to pharmacokinetic studies of ginseng that need further clarification to better understand the safety and possible active mechanism for clinical application. Experimental results demonstrated that ginsenoside metabolites play an important role in the pharmacokinetic properties such as drug metabolizing enzymes and drug transporters, thereby can be applied as a metabolic modulator. Very few are known on the possibility of the consistency of detected ginsenosides with real active metabolites if taken the recommended dose of ginseng, but they have been found to act on the pharmacokinetic key factors in any clinical trial, affecting oral bioavailability. Since ginseng is increasingly being taken in a manner more often associated with prescription medicines, ginseng and drug interactions have been also reviewed. Considering the extensive oral administration of ginseng, the aim of this review is to provide a comprehensive overview and perspectives of recent studies on the pharmacokinetic properties of ginsenosides such as deglycosylation, absorption, metabolizing enzymes and transporters, together with ginsenoside and drug interactions.

1. Introduction

In general, herbal medicines that make up oriental medicine prescriptions have been found to contain various glycoside ingredients. Glycosides of these herbal medicines include ginsenosides, flavonoids, phenols and so on. Recently, it has been reported that these glycoside components are hydrolyzed and absorbed after oral administration, thereby demonstrating true medicinal efficacy. These facts well support that the absorption rate of ginsenosides is very poor, resulting in the difficulty to reach their optimal blood concentration showing pharmacological effects. Moreover, because intestinal bacteria rather than gastric acid are deeply involved in this hydrolysis, the presence or absence of intestinal bacteria with the ability to hydrolyze glycosides is a factor that causes differences in drug efficacy. In other words, it has been suggested that the so-called glycoside, which is said to be effective due to the hydrolysis product of glycoside by intestinal bacteria, is a prodrug [1]. However, in the case of ginseng, unlike drugs containing a single component, it contains various active components, ginsenosides and non-saponin components [2]. And also ginseng shows various pharmacological effects and mechanisms of action, so it is very difficult to scientifically evaluate the pharmacokinetic properties. Pharmacokinetics is the way the body affects the drug with time. It affects not only toxicological actions but also pharmacological effects in the body by biological, physiological and physicochemical factors. Additionally, because chemically transformed or biotransformed products derived from ginseng are taken orally, numerous metabolites are produced by gastric juice or intestinal bacteria in the gastrointestinal tract. Furthermore, the bioavailability due to pharmacokinetic interactions are generally affected by concomitant drugs that can induce or inhibit cytochrome P450 (CYP) or P-glycoprotein (Pgp) [3]. CYP enzyme activity, which is involved in drug metabolism, can affect drug efficacy, and herbs or foods that affect CYP enzyme activity can interact with the drug. A lot of herbal medicine products were thought to interact with prescription drugs secondary to the regulatory action of Pgp, a membrane transport protein, as well as CYP [4]. Drug interactions are associated with pharmacokinetic interactions, where a drug affects the absorption, distribution, metabolism, and excretion of other drugs, thereby changing the blood concentration and clinical response of the

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drug, and pharmacodynamic interactions, which change the pharmacological activity [5]. To ensure the safety of taking ginseng and improve its clinical application, information on ginseng and drug interactions is very important [6]. In this paper, recent research results are discussed with reference to ginsenosides and their metabolites in the gastrointestinal tract and liver, the absorption during oral administration of ginseng, and also on the metabolizing enzymes, transporters, including ginsenoside and drug interaction based on pharmacokinetic properties of ginsenosides. Therefore, this comprehensive review provides useful information based on the results obtained through experimental studies, clinical case reports and clinical trials and also suggests further guidelines for optimal clinical utilization.

2. The deglycosylation of ginsenosides in gastrointestinal tract

2.1. Deglycosylation of ginsenosides by gastric juice

Orally administered ginsenosides must meet gastric juice, digestive and bacterial enzymes in the gastrointestinal tract. Karikura et al. studied the degradation of ginsenoside Rb2 (G-Rb2) in rat stomach (*in vivo*) and 0.1 M HCl (in vitro). When treated with 0.1 M HCl, which has similar acidity to gastric juice, a portion of G-Rb2 was hydrolyzed to 20 (R,S)-G-Rg3. However, G-Rb2 was hardly decomposed in the rat stomach, and a small amount of unknown metabolites, different from the hydrolyzate products in 0.1 M HCl, were observed. The metabolites were identified as four types of compounds. As confirmed by NMR and FAB mass spectrometer, they were 25-hydroxy-23-ene, 24-hydroxy-25-ene, 25-hydroperoxy-23-ene, and 24-hydroperoxy-25-ene derivatives of G-Rb2 derivatives. In this study, 20(S)-protopanaxatriol saponin showed chemical modification of hydrolysis of the C-20 glycosyl moiety and hydration of the side chain, and 20(S)-protopanaxadiol saponin showed chemical modification, oxygenation of the side chain [7]. In addition, Karikura et al. reported that G-Rb1 is hydrolyzed to 20 (R,S)-G-Rg3 in 0.1 M HCl and is mainly hydroperoxided to the 25-hydroperoxy-23-ene derivative of G-Rb1 in the rat stomach [8]. When the water extract of ginseng was treated under acid conditions at 60°C, protopanaxadiol (PPD) ginsenoside was converted into G-Rg3 and Δ20-G-Rg3. However, PPD type G-Rb1, Rb2 and Rc isolated from ginseng were hardly converted to G-Rg3 when treated under neutral conditions. It was confirmed that the conversion rate of ginsenoside to G-Rg3 and Δ20-G-Rg3 increased with increasing temperature and time under acidic conditions [9]. G-Rg1, a protopanaxtriol (PPT) saponin, was easily hydrated to the same prosapogenin in the rat stomach and on 0.1 M HCl. G-Rb1 and G-Rb2 were hardly metabolized in the rat stomach, and a small amount of hydroperoxide derivatives was confirmed (Figs. 1 and 2). However, these ginsenosides were easily hydrolyzed to prosapogenein under 0.1 M HCl [10]. Recently, ginsenosides formed in artificial gastric juice were analyzed by ultra-high-pressure liquid chromatography coupled linear ion trap-orbitrap mass spectrometry (UHPLC-LTQ-Orbitrap MS). The two major species, 20(S), 20(R)-PPT and 20(S), 20(R)-PPD, showed generally similar deglycosylated patterns and also yielded hydrated or dehydrated products. Therefore, it was suggested that the low bioavailability of ginsenoside may be related to the production of degraded ginsenoside by gastric juice [11].

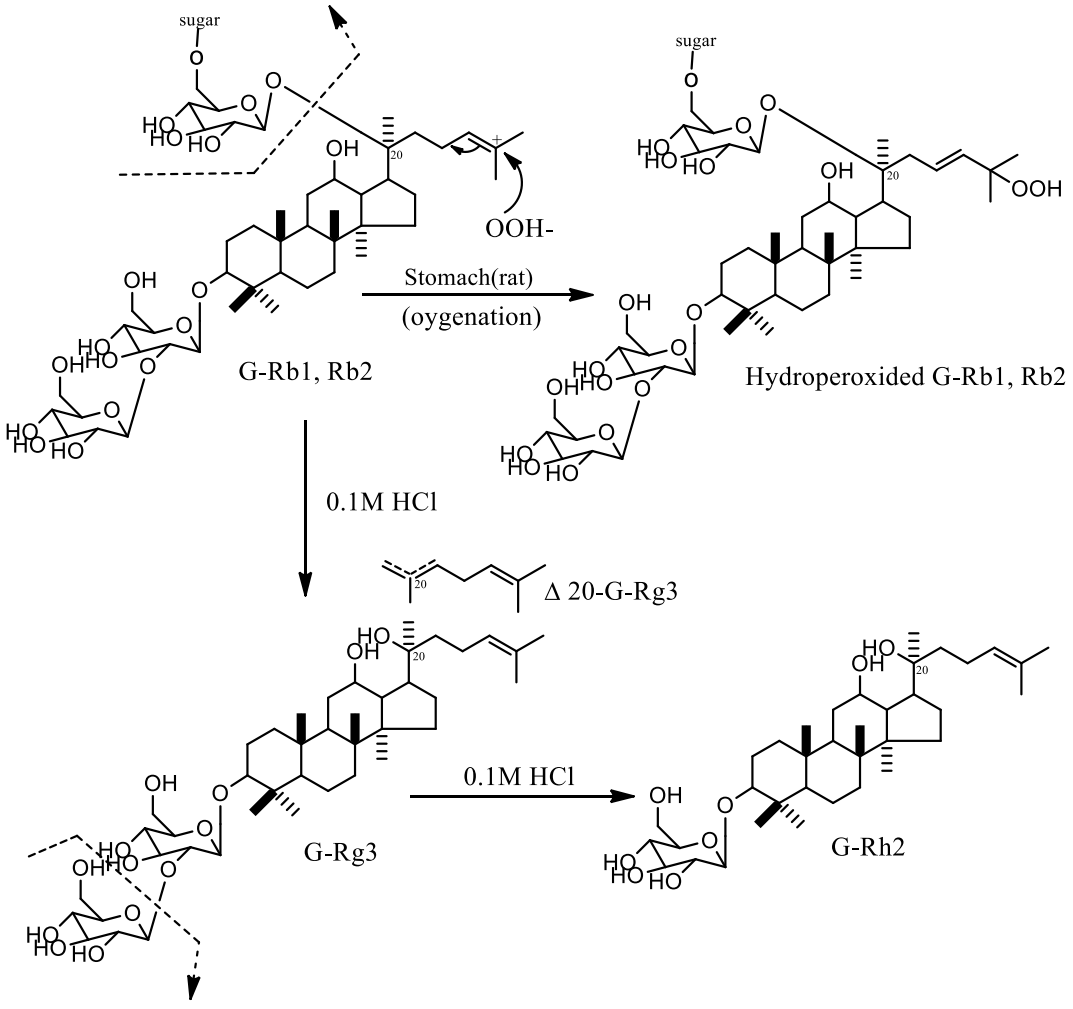

Fig. 1. The possible metabolic pathway of protopanaxadiol ginsenosides by gastric juice in the gastrointestinal tract after oral administration. G: ginsenoside.

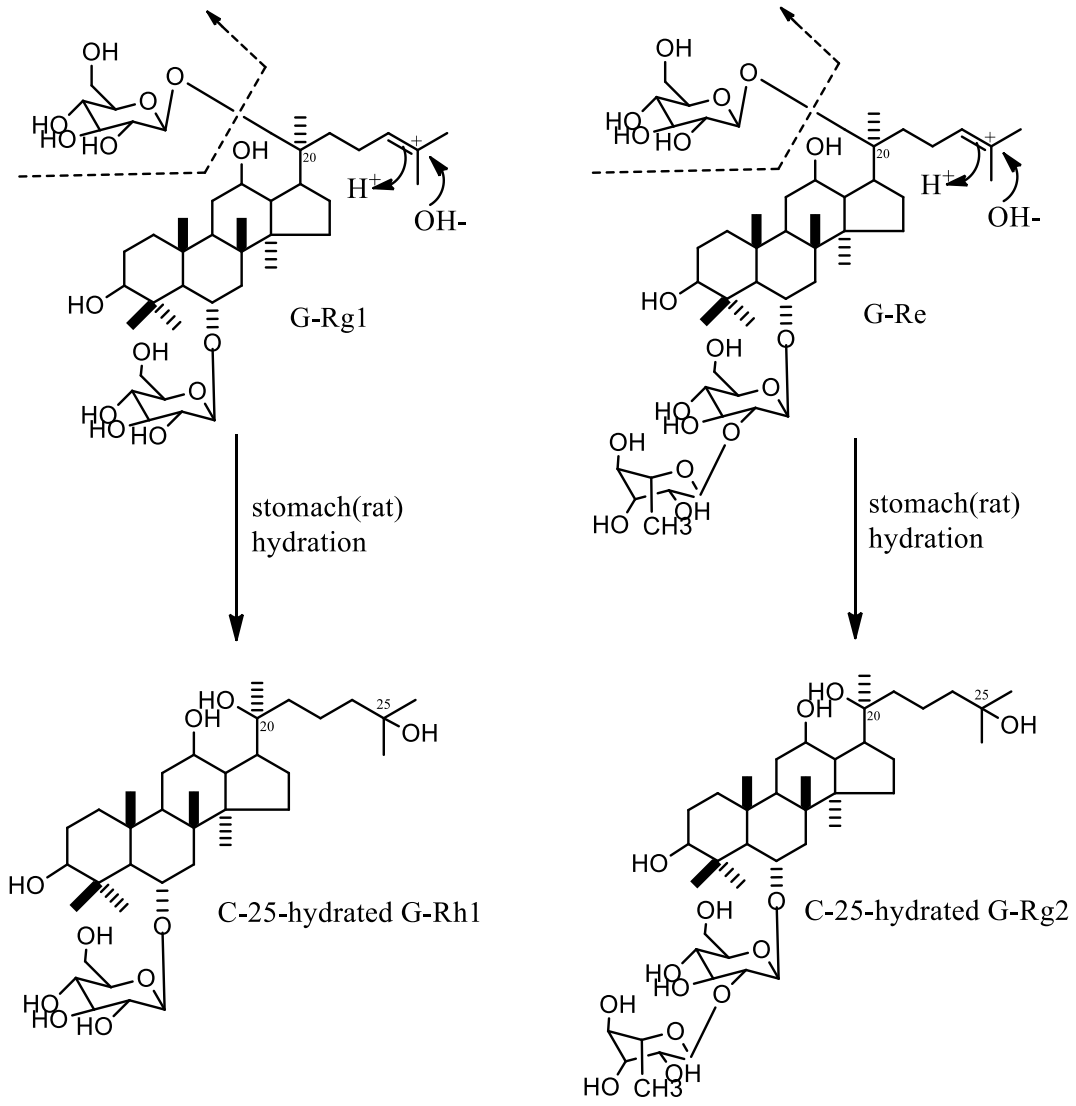

Fig. 2. The possible metabolic pathway of protopanaxatriol ginsenosides by gastric juice in the gastrointestinal tract after oral administration. G: ginsenoside.

2.2. Deglycosylation of ginsenosides by human intestinal bacteria

Although biotransformation characteristics in the gastrointestinal tract have not yet received much attention, it is thought that since more than 1000 species of microorganisms exist in the intestine, they may affect drug metabolism, xenobiotic metabolism and the creation of diseases [12]. It was confirmed that enteric bacteria to hydrolyze naturally occurring G-Rb1 into 20-O-β-D-glucopyranosyl-20(S)-protopanaxadiol (compound K, C–K) were found to be approximately 79% in the feces of 58 people aged 1–64 years [13]. *Prevotella oris* strain was isolated as a major bacterial genus through G-Rb1 hydrolytic activity assay. All intestinal bacteria, like fecal microorganisms, convert G-Rb1 and G-Rd to C–K, and G-Rb2 to compound Y (20-O-[α-L-arabinopyranosyl (1 → 6)-β-D-glucopyranosyl]-20(S)-protopanaxadiol), and G-Rc to M3 (20-O-[α-L-arabinopyranosyl (1 → 6)-β-D-glucofuranosyl]-20(S)-protopanaxadiol). However, it could not convert protopanaxatriol type G-Re or G-Rg1. Taking these results together, it appears that strains metabolizing protopanaxadiol type saponin in the intestines are at least partially caused by *P. oris* present in the intestines. In addition, several types of intestinal microorganisms have been found to hydrolyze natural ginsenoside. *Eubacterium* sp. and *Streptococcus* sp. which can hydrolyze gentibiose more strongly than sophorose, and also *Bifidobcterium* sp. have been shown to metabolize G-Rb1 to C–K via G-Rd rather than gypenoside XVII. However. Fusobacterium K-60, which can hydrolyze sophorose more strongly than gentibiose, converted G-Rb1 to C–K via gypenoside XVII. G-Rb2 was metabolized into G-Rd or compound O by human intestinal microorganisms. *Eubacterium* sp., *Streptococcus* sp. and *Bifidobacterium* sp. metabolically converted G-Rb2 to C–K via G-Rd rather than compound O. Whereas, *Fusobacterium K-60* decomposed G-Rb2 to C–K via compound O [14]. The pattern of ginsenoside metabolite showed no difference even when ginseng water extract was administered instead of the purified ginsenosides. Enzyme activity did not differ depending on gender and age, but there was a significant difference depending on the individual [15].

A portion of G-Rb2 was decomposed in the rat colon, and six types of decomposition products were confirmed by TLC (Thin Layer Chromatography). Among them, 5 species were isolated: G-Rd, 3-O-β-D-glucopyranosyl-20-O-[α-L-arabinopyranosyl (1 → 6)-β-D-glucopyranosyl]-20 (S)-protopanaxadiol. As for the rest, they were identified as G-F2, 20-O-[α-L-arabinopyranosyl (1 → 6)-β-D-glucopyranosyl]-20(S)-protopanaxadiol, and C–K, respectively [16]. Additionally, five types of degradation products of G-Rb1 were observed in the large intestine of rats and identified as gypenoside XVII, G-Rd, G-F2, C–K, and gypenoside LXXV. The *in vivo* degradation modes of G-Rb1 and G-Rb2 are thought to be different due to the hydrolysis rate of the terminal sugar moiety at the C-20 hydroxyl group [17]. When G-Rc was cultured with human fecal

microorganisms under anaerobic conditions, it was converted into the major metabolites, C–K and PPD. Most microorganisms in human stool include *Bacteroides* sp., *Eubacterium* sp. and *Bifidobacterium* sp. *Bifidobacterium K-103* and *Eubacterium A-44* converted G-Rc to C–K via G-Rd, and *Bacteroides HJ-15* and *Bifidobacterium K-506* converted it to C–K via G-Mb [18]. The degradation mode of G-Rg1, a representative component of PPT saponin, by human or rat intestinal bacteria was identified by TLC and EI-Mass *in vitro* and *in vivo*. It has been shown that G-Rg1 is converted into two metabolites, G-Rh1 and 20(S)-PPT, by human intestinal bacteria in vitro, while it is converted to three metabolites by rat intestinal bacteria in vitro and *in vivo*. The species of G-Rh1, G-F1, and 20(S)-PPT were detected. In summary, the metabolic process of G-Rg1 in the rat intestine was G-Rg1 → G-Rh1 (G-F1) → PPT [19]. When ginseng water extract was treated under acidic conditions, PPD ginsenosides were converted to G-Rg3 and Δ20-G-Rg3. The converted G-Rg3 and Δ20-G-Rg3 were converted to G-Rh2 and Δ20-G-Rh2, respectively, by human fecal microorganisms. Microorganisms isolated from human fecal microorganisms include *Bacteroides* sp., *Bifidobacterium* sp. and *Fusobacterium* sp., which strongly converted G-Rg3 to G-Rh2 [20]. The main metabolic pathways of ginsenoside by intestinal bacteria are as follows. PPD type: G-Rb1 → G-Rd → G-F2 → C–K, G-Rb2 → C–Y → C–K, G-Rc → G-Mb → G-Mc → C–K and C–K is gradually hydrolyzed to PPD. PPT type: G-Re → G-Rg1 → G-F1 or G-Rh1 → PPT, G-Rg1 → G-F1 or G-Rh1 → PPT [21]. The main metabolic pathways of PPD and PPT ginsenosides are summarized (Figs. 3 and 4).

In fact, ginsenoside metabolites caused by microorganisms are absorbed into the blood instead of ginsenosides that exist naturally. Similarly, in a case report, a single-sequence study has been recently conducted in which red ginseng extract and lactic acid bacteria were simultaneously administered to five healthy men. As a result, the deglycosylation metabolism of ginsenoside was enhanced in the intestine and the plasma concentrations of G-Rh2, C–K, PPD and PPT were increased [22]. Accordingly, it is believed that active metabolites, a decomposition product of ginsenoside by intestinal microorganisms,

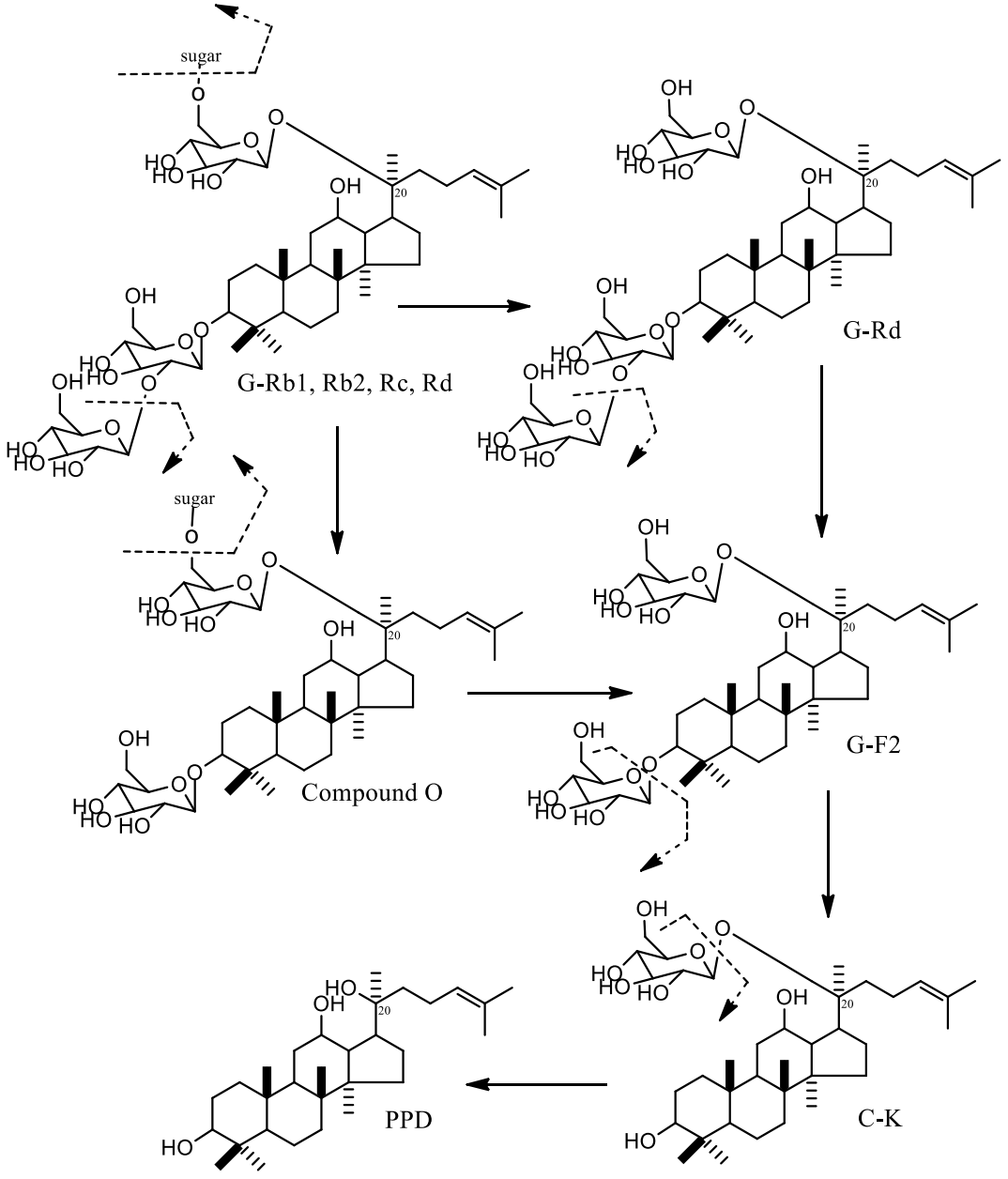

Fig. 3. The possible metabolic pathway of protopanaxadiol ginsenosides by human intestinal bacteria in the gastrointestinal tract after oral administration. G: ginsenoside, Cpd: compound, PPD: protopanaxadiol, C–K: compound K.

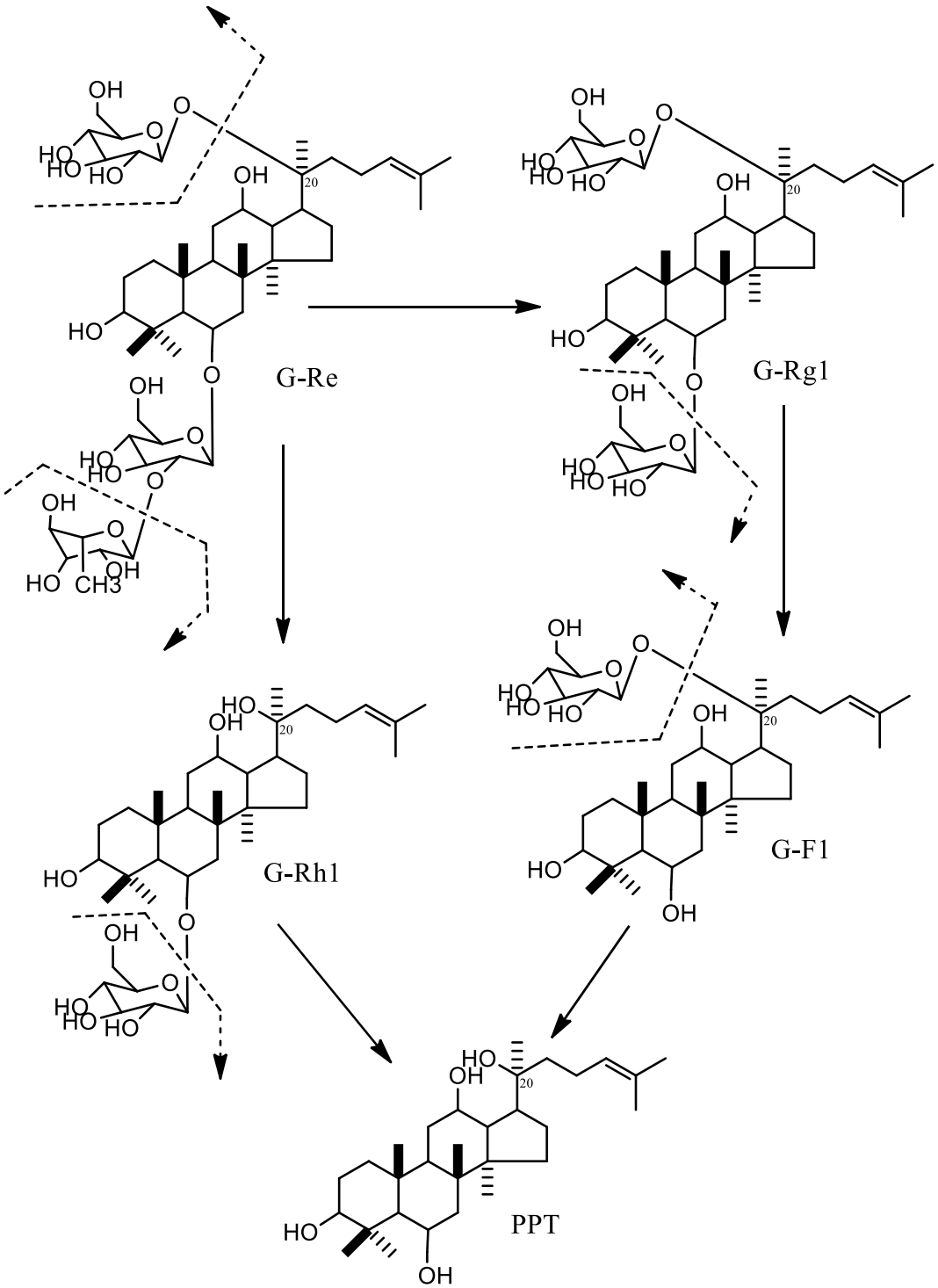

Fig. 4. The possible metabolic pathway of protopanaxatriol ginsenosides by human intestinal bacteria in the gastrointestinal tract after oral administration. G: ginsenoside, PPT: protopanaxatriol.

will play an important role for mechanism of action in the human body [23].

3. The absorption of ginsenosides from gastrointestinal tract

3.1. The absorption of naturally occurring ginsenosides

Most ginseng products are composed of naturally occurring saponin components such as G-Rb1, G-Rb2, G-Rc, G-Rd, G-Re, G-Rf and G-Rg1, but most of them are hardly absorbed in the gastrointestinal tract. After oral administration of red ginseng extract to healthy volunteers, the plasma concentration of ginsenoside was measured by EIA-HPLC, and G-Rb1 was hardly detected in the blood [24]. When G-Rb1 was administered orally at the dose of 200 mg/kg to rat without microorganisms, not only C–K but also any metabolites were detected in the plasma. Most of G-Rb1 remained in the intestinal tract and showed a low absorption rate [25]. In addition, even after oral administration of G-Rb1 (125 mg/kg) to mice, neither G-Rb1 nor intermediate metabolic derivatives were

detected in the blood, and only C–K was finally detected at a concentration of 1.0–7.3 μg/mL [26]. Xu et al. also reported that the absorption rate of G-Rb1 was 4.35% and that of G-Rg1 was 18.4% as a result of HPLC analysis [27]. G-Rg3 was not detected in rat plasma after oral administration (100 mg/kg). Only 0.97–1.15% of administered G-Rg3 was observed in feces [28], and the maximum plasma concentration-time was 16 ng/mL upon single oral administration (3.2 mg/kg) to eight healthy male volunteers. In six other volunteers, G-Rg3 was not detected in the plasma when administered orally at 0.8 mg/kg [29]. These results suggest that the absorption of naturally occurring ginsenoside is very low and that the plasma concentration does not reach the required concentration to show pharmacological efficacy. The bioavailability of ginsenoside in white ginseng and red ginseng was measured using the simulated digestion Caco-2 cell culture model. Regardless of the ginsenoside composition of white and red ginseng, good bioaccessibility of about 85% was confirmed in the last ileum phase, but low absorption rate was shown in the Caco-2 cell culture model [30]. Pan et al. attempted various methods such as nanoparticles, liposomes, emulsions and micelles to overcome the low absorption rate of ginsenoside in the gastrointestinal tract. In particular, the development of pseudoginsenoside F11, an ocotillol type ginsenoside, showing anti-Alzheimer's disease activity, suggested the possibility of improving the absorption rate of ginsenoside [31]. Recently, Wang et al. suggested the possibility of acid and base hydrolysates, 20 (R,S)-panaxadiol and 20 (R,S)-PPD, to improve the low absorption rate and bioavailability of ginsenoside. The result showed that it is necessary to apply them to clinical research of antitumor pharmacological activity through increased absorption of structurally modified derivatives with active group at the C-3 position [32].

3.2. The absorption of ginsenoside metabolites

Paek et al. performed a permeability assay with Caco-2 cell monolayer and found that the absorption of C–K, a major intestinal ginsenoside metabolite, showed moderate permeability without any directional effect, suggesting passive diffusion [33]. After oral administration of ginseng total saponin to rats, C–K and PPD were detected in the blood along with PPT. Their intestinal absorption rate was increased in a time-dependent manner. After oral administration of ginseng extract (150 mg/kg/day) to humans, C–K was detected at approximately 0.2 μg/mL within 16–24 h [34]. Looking at the results of another pharmacokinetic study after oral administration of G-Rb1 and C–K, in the case of G-Rb1, the level of C–K in the blood showed a maximum of 8.5 μg/mL at 8 h, but in the case of C–K, it reached a maximum of 8.5 μg/mL at 2 h, showing a maximum of 10.3 μg/mL [35]. After oral administration of standardized Ginsana extract G115, two hydrolyzed products of PPT ginsenosides, G-Rh1 and G-F1, were detected in the circulation. In addition, C–K was detected in plasma and urine, and G-Rb1 was only identified in the urine and plasma of one person, but quantitative research results were not presented. These results showed that the decomposition products of ginsenoside have higher permeability than naturally occurring ginsenoside. However, since there is no direct comparison between ginsenosides that exists in nature and these metabolites, more extensive research will be necessary [36]. Ginsenoside metabolites, G-Rg3, G-Rg5, G-Rk1, C–K, G-Rh1, G-F2 and G-Rg2 of red ginseng extract fermented by *Phellinus linteus* showed high bioavailability in skin permeation and intestinal permeability. It appears to be due to biological conversion [37]. Kim et al. conducted an open-label, single-oral dose pharmacokinetic study by orally administering red ginseng extracts of G-Rb1 and its metabolite C–K to 10 healthy men. Mean maximum plasma concentration was 8.35 ± 3.19 ng/mL for C–K and 3.94 ± 1.97 ng/mL for G-Rb1. The half-life of C–K was 7 times higher than that of G-Rb1. The absorption of C–K was not affected in any way by G-Rb1, and it was concluded that the delayed absorption may play an important role in the bioconversion of G-Rb1 to C–K by intestinal microorganisms [38].

Besides fermented ginseng was administered to 12 healthy Japanese people and an open-label, a randomized, single-dose, two-period, crossover study was performed. In the case of fermented ginseng, C–K was 17.5–58.3 times higher than that of non-fermented ginseng in terms of area under the curve (AUC) (0–12 h, ng/mL) and AUC (0–24 h, ng/mL), and the main lactic acid bacteria of ginseng was *Lactobacillus paracasei* A221. It was claimed that C–K might be an active ginsenoside that is important for maintaining health [39]. Continually, it was also demonstrated that ginsenosides are converted to C–K, PPD and PPT by the action of probiotics such as *Bacteroides, Eubacterium, Bifidobacterium* and *Fusobacterium*, suggesting the improved absorption rate to increase the pharmacodynamic value of ginseng [40].

4. Metabolism of ginsenosides by liver enzymes

Drugs given orally are usually absorbed in the small intestine and enter the portal system to travel to the liver, where they may be extensively metabolized. To date, there is little information available on the metabolism of ginseng saponins by liver enzymes. Hasegawa et al. reported that when C–K was injected intravenously in C57BL/6 mice and Wistar rats, some of it was selectively accumulated in the liver and most of it was excreted in bile as a prototype. However, some C–K was esterified in the liver to mono-fatty acid esters (EM1). EM1 was isolated from rat liver with a recovery rate of almost 24 mol%. It was not excreted in bile like C–K and accumulates longer than C–K in the liver [41]. PPT is a major microbial metabolite of protopanaxatriol-type ginsenosides. Orally administered PPT is absorbed from the small intestine into mesenteric lymphatic vessels and is quickly esterified into fatty acids, accumulated in the liver [42]. Hao et al. conducted a study on the hepatic cytochrome P450-catalyzed metabolism of PPT ginsenoside. CYP3A4 was identified as an important isozyme in the oxygenation metabolism of PPT ginsenoside. In particular, glycosyl substitution at the C-20 hydroxyl group shows the hepatic disposition of ginsenoside, which determines intrinsic clearances by CYP3A4 in the order of G-Rf < G-Rg2 < G-Rh1 < PPT [43]. SIRT1 is an enzyme located in the cell nucleus that deacetylates transcription factors that contribute to cellular regulation (reaction to stressors, longevity). SIRT1-activating metabolite has been recently searched in the rat liver microsome incubation system of 20(S)-G-Rg2. A new metabolite of 20(S)-G-Rg2, ginsenotransmetin A (M1) was elucidated as 6-O-α-L-rhamnopyranosyl-(1 → 2)-β-D-glucopyranosyl-dammar-24Z-ene-3β,6α,12β,20(R),27-pentol.
And the additional mono-, dioxidation and cyclization metabolites, M2 (20(R)-G-Rg2), M3 (pseudoginsenoside F11) and M4 (20(R)-pseudoginsenoside F11), were identified as SIRT1 activators (Fig. 5). This metabolite has shown the potential to be developed as a lead molecule for the development of new drugs that can treat aging diseases related to SIRT1 activation in the future [44].

5. Pharmacokinetic properties of ginsenosides

Over the past decades, various studies addressing the pharmacokinetics of ginsenosides have been conducted, and it has been proven that the decomposition patterns are different depending on the PPD and PPT types. G-Rb2 had an absorption rate of 3.7% when immunochemical analysis was performed using ^{3}H-labeled G-Rb2. When G-Rg1 was orally administered to rats at a single dose of 100 mg/kg, 0.4% was excreted in urine and 1.1% in bile [45]. More recently, when red ginseng extract containing radioactively labeled ^{3}H-labeled ginsenoside was orally administered to Sprague-Dawley rats at a dose of 10 mg/kg, pharmacokinetic properties of metabolites have been recently reviewed. As a result, C_{max} (maximum concentration) and half-life were increased, and T_{max} (the time-to-maximum) were decreased. G-Rb1 and C–K showed similar properties. The cumulative excretion ratio of urine and feces was 88.9–92.4%, and even though it was excreted within 96–168 h, the active component was detected in small amounts in all tissues and was mainly distributed in the liver except the digestive tract, confirming the

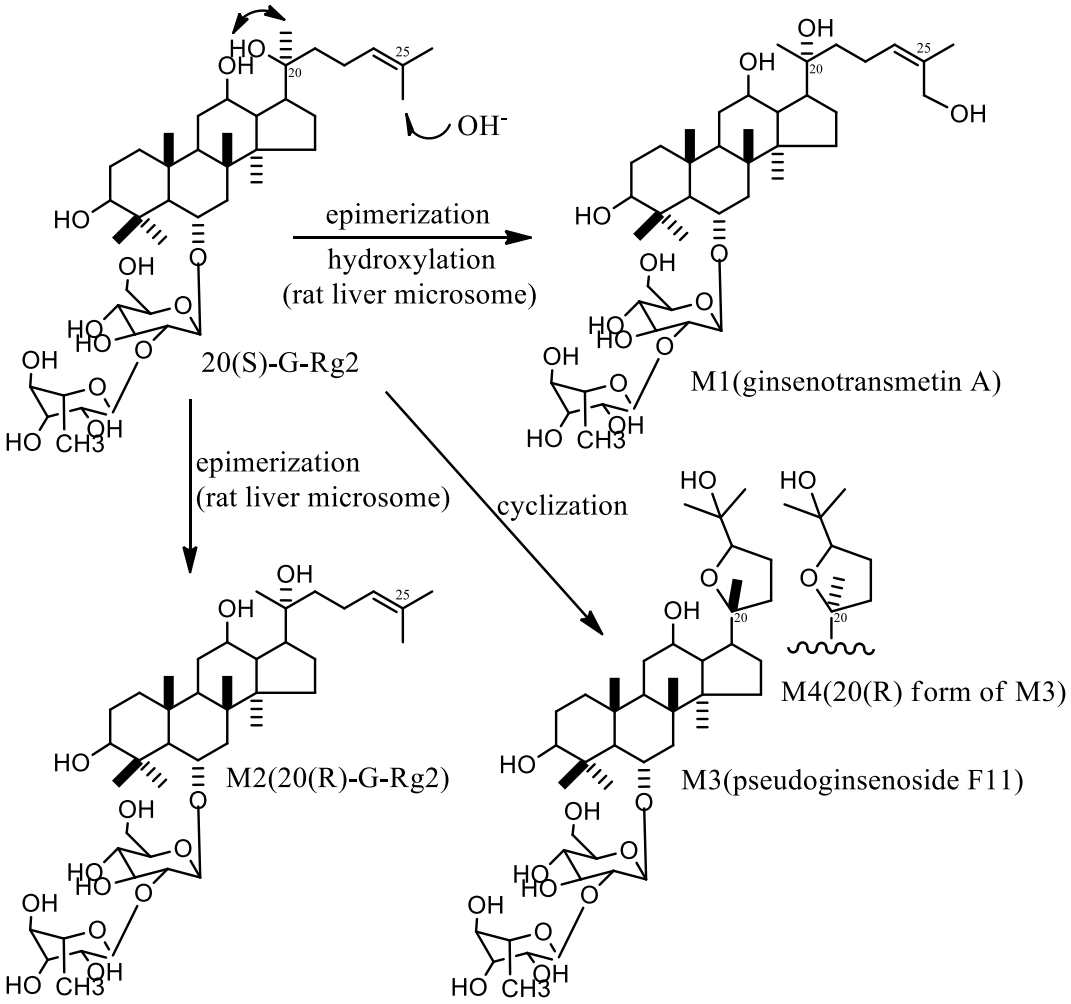

Fig. 5. The proposed possible metabolic pathway of 20(S)-G-Rg2 by rat liver microsome. G: ginsenoside, M: metabolite.

pharmacokinetic properties related to the mechanism of action of red ginseng [46]. A randomized, open-label, 2-treatment, 2 × 2 crossover study has been conducted on the pharmacokinetic properties of C–K from Korean red ginseng and fermented red ginseng (CK-30) in healthy Korean subjects. When 2.94 g of red ginseng was administered as a single dose, the average time to reach C_{max} was 3 h for CK-30 and 10 h for red ginseng. In addition, C_{max} and AUC were 118.3 and 135.1 times higher for CK-30 than those of red ginseng, respectively, suggesting high bioavailability of fermented red ginseng (CK-30) [47]. However, in order to evaluate the various health promoting activities and safety of C–K, more extensive preclinical and clinical studies need to be performed [48]. Meanwhile, Chen et al. reviewed the pharmacokinetic properties and tissue distribution of white ginseng (WG), frozen ginseng (FG) and red ginseng (RG) according to processing methods. The AUC of G-Rg1, G-Re, G-Rb1 and G-Rd were higher than that of pure ginsenoside and showed differences depending on the processing method. The amounts of G-Rg1, G-Re, G-Rb1 and G-Rd were high in tissues. In particular, the amounts of G-Re, G-Rb1 and G-Rd in RG were significantly high in the heart, lungs, and kidneys. Therefore, it was confirmed that the processing method of ginseng affects pharmacokinetics and oral bioavailability [49]. In another study, after oral administration of Korean red ginseng and fermented red ginseng to 34 healthy Korean people, Kim et al. investigated the correlation between the pharmacokinetic properties of G-Rd, G-Rg3, G-F2 and C–K and the ginsenoside metabolizing activity of human fecal microbiota. It was found that enzymes of intestinal microorganisms are mainly involved in the bioconversion of ginsenosides, focusing on C–K, and the composition of intestinal microorganisms was confirmed to affect the bioavailability and pharmacological activity of ginsenosides [50]. Won et al. presented the pharmacokinetic characteristics of ginsenoside according to the route of administration in various animal models and suggested the need to optimize the optimal dosage form and delivery system of ginsenoside to overcome the low bioavailability of ginsenoside and maximize clinical usefulness [51]. And also, it has been observed that a drug delivery system and chemical conversion are needed to overcome the low absorption rate of G-Rb2, a major saponin of ginseng, and that the therapeutic effect should be reevaluated through clinical research [52]. A randomized, open label, single-dose, single-sequence crossover study was carried out after one-time oral administration of RG (red ginseng) and BRG (bioconverted red ginseng extract) to 13 healthy Korean men. The bioactive ginsenosides of G-Rg3, G-Rk1 + G-Rg5, G-F2 and C–K showed higher C_{max}, AUC(0-t), AUC(0-∞) and shorter T_{max} in the BRG group than those in the RG group. These results confirmed the high absorption rate of bioactive ginsenoside in human experiments and provided valuable information to enhance the therapeutic effect and pharmacological activity of ginseng [53]. From these research results, it is expected that the true active metabolites will be identified in the future and can further be used as a marker of the pharmacokinetic properties of ginseng or related products.

6. Effects of ginseng on drug metabolizing enzymes and drug transporter

6.1. Modulation of ginseng on cytochrome P450 isoforms (CYPs) in vitro and in vivo

Drug metabolism represents an important process by which drugs are eliminated from the body. Such drugs are mainly eliminated by cytochrome P450 (CYP) and undergo Phase I metabolism. CYP3A4 is the most important CYP isozymes (CYPs) and is involved in most metabolism and more than 50% of all prescription drugs are metabolized by CYP3A4 [54]. In experiments using human liver microsomes and cDNA expressed CYP3A4, G-Rb1 had no significant effect, but G-Rh1 and G-F1 showed a competitive inhibitory effect on the CYP3A4 enzyme. In particular, the ginsenoside aglycones, 20(S)-PPD and 20(S)-PPT was found to show competitive inhibitory activity on CYP3A4 activity. However, the IC_{50} value of PPD and PPT were extremely high at 14.1 ± 2.3 μM and 7.1 ± 0.9 μM on CYP4A4, respectively, compared to the positive control drug (ketoconazole: 0.06 ± 0.01 μM) [55]. In rat liver microsomes, G-Rb1, G-Rb2, G-Rc, C–K, G-Re and G-Rg1 did not show an inhibitory effect on CYP3A enzyme activity, but G-Rg2 showed a weak inhibitory effect, while PPT, a strong competitive inhibitory activity [56]. In another study, C–K, a major intestinal bacterial metabolite, inhibited CYP3A4 and CYP2C9 enzyme activities in human recombinant CYPs. The IC_{50} on enzyme activity of CYP2C9 and CYP3A4 in human microsomes was 16.00 μM and 9.83 μM, respectively, showing strong inhibitory activity. However, it had little effect on CYP1A2, CYP2A6, CYP2D6, CYP2E1 and CYP2C19 [57]. In a study on the activity of human CYPs involved in PPD metabolism in human colonic and liver microsomes, CYP3A4 showed the highest activity in forming oxidants, which are biological variants, among the combined human CYPs enzymes. It was confirmed that it acts as a substrate for CYP3A4, suggesting that PPD might cause drug interactions when used in combination with other treatments [58]. And also, PPD and PPT have been shown to exhibit the inhibitory effect on the breakdown (inactivation) of active Vitamin D3 mediated by CYP3A4 in the human liver and intestines [59]. In particular, the inhibitory activity of ginsenoside and sapogenin on CYP3A4 has been found to be decreased as the number of glycosyl moieties increase. Moreover, it was found that the activity of deglycosylated ginsenoside metabolites was stronger than that of glycosylated ones, indicating that a structure-activity relationship exists between CYPs enzyme activity and ginsenoside structure [60,61]. Lee et al. have recently conducted a combined asdministration of PPD(70 mg/kg) and felodipine, an antihypertensive agent metabolized by CYP3A, at 10 mg/kg to mice to examine the inhibitory effect of PPD on CYPs. It was confirmed that PPD affects the metabolism of CYP3A4 and CYP2B6, recommending that caution should be exercised in co-administration with other drugs [62] (Table 1).

Table 1
In vitro and *in vivo* modulation of Cytochrome P450(CYP) by ginseng.

Compound type	System	Effects	Ref
G-Rg2, G-F1	Rat liver microsome	CYP3A ↓	[56]
C–K	Human recombinant CYPs	CYP2C9 ↓, CYP3A4 ↓	[57]
20(S)-PPD	Human intestinal microsomes (HIM), Human liver microsomes (HLM)	CYP3A4 ↑, CYP3A5 ↑	[58]
20(S)-PPD, 20(S)-PPT	Human hepatic or intestinal microsomal protein	CYP3A4-mediated catabolism of active vitamin D3 ↓	[59]
Ginsenosides and sapogenin	Human recombinant CYPs	G-Rb1, G-Rd, G-Re, G-Rg2, G-Rg1: CYPs ↓ C–K: CYP1A2 ↓, CYP3A4 ↓ G-Rg3: CYP2D6 ↓	[60]
Ginsenosides	HepG2 cells	Deglycosylated ginsenosides: CYP1A1, CYP1A2, CYP3A4 ↑	[61]
20(S)-PPD	Human liver microsome Mouse liver microsomes	CYP3A4 ↓(human liver microsome) CYP3A, CYP2B ↓(mouse liver microsome)	[62]

G: ginsenoside, C: compound, PPD: protopanaxadiol, PPT: protopanaxatriol, ↑: upregulation, ↓: downregulation.

6.2. Modulation of ginseng on P-glycoprotein (Pgp) in vitro and in vivo

Pgp is widely distributed in intestinal endothelial cells and excretes foreign substances (toxic substances or drugs) into bile ducts from hepatocytes, into proximal tubules from proximal tubular cells of the kidney, and into capillaries from the blood brain barrier (BBB). Therefore, simultaneous administration of Pgp inhibitors and substrates may increase bioavailability and absorption, resulting in increased side effects or toxicity due to changes in pharmacokinetics [63]. Transport and uptake experiments of Pgp by ginsenosides were conducted using Caco-2 and L-MDR1 cells. G-Rb2, -Rc, -Rg2, -Rg3, -Rd and -Rb1 were confirmed to act as Pgp substrates, and the absorption of these ginsenosides was significantly increased by verapamil (Pgp inhibitor) [64]. In the case of 20(S)–Rh2, it inhibited Pgp non-competitively when administered long-term to rats (25 mg/kg, 10 days) [65]. In experiments with nude mice and rats transplanted with human breast cancer cells (MCF-7), G-Rg3 has been shown to enhance the antitumor effect of paclitaxel and increase bioavailability [66]. Yang et al. reported that the low bioavailability of C–K, below 5.0% when administered orally, is because it acts as a substrate for Pgp and is hindered by the excretion of Pgp [67]. Ginsenoside metabolites, such as PPT type ginsenosides, G-F1, PPD and PPT, were found to reduce the excretion rate of digoxin and inhibit Pgp, suggesting drug interaction [68]. Xiong et al. have recently reported that combined administration of verapamil, a G-Rg3 and Pgp inhibitor, lowered G-Rg3 efflux and increased absorption in the small intestine in a benzopyrene-induced tumorigenesis rat model. Therefore, the important role of Pgp to enhance the oral bioavailability of ginsenoside has been emphasized [69] (Table 2).

6.3. Modulation of ginseng on cytochrome P450 isoforms (CYPs) and P-glycoprotein (Pgp) in clinical studies

Some clinical research results on CYPs and Pgp have been so far

Table 2
In vitro and *in vivo* modulation of P-glycoprotein (Pgp) by ginseng.

Compound type	System	Effects	Ref
G-Rb1, G-Rb2, G-Rc, G-Rd	Caco-2 cell, L-MDR1 cell	Pgp↑	[64]
20(S)-G-Rh2	Caco-2 cell (in vitro) Rats (*in vivo*): probe drug (Digoxin)	Pgp ↓ (Cmax & AUC↑)	[65]
20(S)-G-Rg3	Caco-2 cell (in vitro) Rat and nude mice (*in vivo*) Probe drug: Paclitaxel	Pgp ↓ (Paclitaxel bioavailability↑)	[66]
G-Rg3	Tumorigenesis rat (benzopyrene) Probe drug: verapamil	Pgp ↓ (oral bioavailability↑)	[69]
C–K	Caco-2 cell (in vitro) Mdr1 a/b (−/−)FVB mice (*in vivo*)	Pgp ↑ (Cmax & AUC↓)	[67]
G-F1	Caco-2 cell, MDR1-MDCK cell (digoxin transport assay)	Pgp ↓	[68]
PPD, PPT	Caco-2 cell (in vitro) Intestinal perfusion assay (in situ)	Pgp ↓ (Digoxin efflux↓)	[68]

G: ginsenoside, C: compound, PPD: protopanaxadiol, PPT: protopanaxatriol, Cmax: the maximum concentration, AUC: the area under the curve, ↑: upregulation, ↓: downregulation.

reported. Gurley et al. administered 500 mg of a ginseng product, standardized to 5% ginsenoside, twice a day for 28 days to young healthy subjects (n = 12). Before and after administration, a mixture of midazolam, caffeine, chlorzoxazone, debrisoquin INN and debrisoquine was administered as a CYP probe drug. Among each blood sample, 1-hydroxymidazolam/midazolam, paraxanthine/caffeine, 6-hydroxychlorzoxazone/chlorzoxazone and debrisoquine urinary recovery ratios were tested as evaluation indicators on CYP3A4, CYP1A2, CYP2E1 and CYP2D6 enzyme activities However, ginseng has been found to show no significant effect on CYP activity [70]. In addition, Anderson et al. reported that a ginseng product (500 mg, twice daily, 14 days), standardized to 4% ginsenoside, has not been found to show no significant influence in a clinical trial evaluating CYP3A activity using the 6-β–OH–Cortisol/Cortisol Ratio in healthy volunteers [71]. In another clinical trial on ginseng's CYP3A and Pgp functions, an inducing effect of ginseng on CYP3A enzyme was observed. The AUC of midazolam in the blood was calculated by collecting blood from 12 healthy volunteers 24 h after midazolam administration. In a clinical trial evaluating CYP3A4 activity, it was reported that when taking a ginseng product standardized with 5% ginsenosides (500 mg, twice daily, 28 days), the AUC of midazolam, a CYP3A4 indicator drug, decreased by 34%, showing an inducing effect on CYP3A4 [72]. Recently, Kim et al. have evaluated the effects of red ginseng and fermented red ginseng on CYPs and Pgp. In an open-label crossover study, a cocktail technique was used with 15 subjects each assigned to the red ginseng group and the fermented red ginseng group before and after taking red ginseng and fermented red ginseng for 2 weeks. A combination of caffeine, losartan, dextromethorphan, omeprazole, midazolam and fexofenadine were administered as indicator drugs, and pharmacokinetic blood and urine collection were performed. Pharmacokinetic parameters were calculated by measuring blood drug concentration and the effect was tested by calculating the 90% confidence interval of the geometric mean ratio after ingestion compared to before ingestion of red ginseng and fermented red ginseng. As a result of the experiment, red ginseng and fermented red ginseng did not affect CYP2C19 and CYP2D6, and inhibited CYP1A2, CYP2C9 and CYP3A4, but the magnitude of the effect was so small that it was considered to have no clinical significance. Additionally, red ginseng did not affect Pgp. In the case of fermented red ginseng, the AUC of fexofenadine was increased by 32% after consumption compared to before consumption, confirming clinically significant inhibition of Pgp. Therefore, caution seems to be required when using fermented red ginseng in combination with Pgp substrate drugs as there is a possibility of increasing systemic exposure to the drug [73,74](Table 3).

7. Clinical trials and case reports of ginseng-drug interactions

Although several clinical studies have been reported on the interactions between ginseng and prescription drugs, very little information is available in the literature with regard to statistically significant interactions.

7.1. Interaction with anticancer drugs

In general, in the case of cancer patients, the combined use of herbal remedies and anticancer drugs is almost common, so the possibility of drug interactions is considered to be higher. Ginsenoside and polysaccharide of Korean ginseng have been found to show various antitumor activities such as inhibition of angiogenesis, activation of natural killer cells and apoptosis [75]. Drug interactions between ginseng and imatinib, which is used as an anticancer drug, have been reported. In a chronic myeloid leukemia (CML) patient (26-year-old male) who had been taking imatinib (400 mg/day) for 7 years, the increased liver toxicity was observed after consuming ginseng energy drink, so it was recommended to avoid ginseng products while taking imatinib. This induction of liver toxicity was thought to be due to drug interaction between ginseng and imatinib through inhibition of CYP3A4 enzyme activity [76]. Additionally, a moderate interaction was found with ginseng and procarbazine, which worsened insomnia, tremors, headaches, agitation and depression, suggesting that ginseng increases GABA metabolism and can affect corticoid production [77]. Ginseng has been known to show an estrogen effect, so it has useful effects such as improving menopausal symptoms [78]. On the other hand, there are concerns that cancer patients who are sensitive to hormones should avoid estrogen due to its increased risk of cancer [79]. In contrast, a cohort study reported that the risk ratio of developing secondary endocrine cancer in breast cancer patients who consumed herbal medicine products including ginseng after administration of tamoxifen, a competitive inhibitor of estrogen, was reduced compared to the non-administered group [80]. Moreover, in a cohort study of breast cancer patients (n = 1455), the quality of life (QOL) was improved and

Table 3
Clinical trial modulation on Cytochrome P450(CYP) and P-glycoprotein (Pgp) by ginseng.

Study design	Ginseng types/Dosage	Interacting drugs	Effects	Reference
Healthy volunteers (n = 12) (Non-controlled open study)	Ginsana (standardized 5% ginsenosides), 500 mg, three times daily for 28 days	Probe drug cocktails: midazolam (CYP3A4) + caffeine (CYP1A2) + chlorzoxazone (CYP2E1) + debrisoquine (CYP2D6)	No significant effect on CYP activity, No effect on pharmacokinetics of probe drugs	[70]
Healthy volunteers (n = 20)	Ginseng extract (4% ginsenosides), 100 mg orally, twice daily, for 14 days	6-β-hydroxycortisol/cortisol ratio as amarker of CYP3A	No significant effect on CYP3A	[71]
Healthy volunteers (n = 12) (Non-controlled open study)	Ginseng extract (500 mg orally, twice daily, for 28 days)	Midazolam (CYP3A probe substrate): 8 mg, Fexofenadine (Pgp probe substrate): 120 mg, single oral dose	CYP3A activity↑ Pgp: no effect Fexofenadine: no significant changes in pharmacokinetics	[72]
Healthy male volunteers (n = 14) (Open-label, crossover study)	Red ginseng extract (10 mL/day, 14 days)	CYP probe drug cocktail (caffeine + losartan + omeprazole + dextromethorphan + midazolam + fexofenadine), administered before and after ginseng supplementation	No relevant potential to cause CYP or Pgp related interaction	[73]
Healthy male volunteers (n = 14) (Open-label, crossover study	Fermented red ginseng extract (70 mL/day, 14 days)	CYP probe drug cocktail (caffeine + losartan + omeprazole + dextromethorphan + midazolam + fexofenadine), administered before and after ginseng supplementation	No significant drug interactions between fermented red ginseng and the CYP probe substrate, Pgp activity↑	[74]

↑: upregulation, ↓: downregulation.

the relative mortality risk ratio was reduced in the ginseng consumption group (n = 398) compared to the non-consuming group (n = 1057) [81].

7.2. Interaction with warfarin

Warfarin is an antagonist of vitamin K that activates blood coagulation factors to quickly coagulate blood during bleeding and is widely used as an oral anticoagulant drug. However, warfarin is a narrow therapeutic index drug and may have a tendency to interact with drugs or foods and cause bleeding. In a case report, a possible drug interaction was reported between ginseng and warfarin, which is used as an antithrombotic agent. In a patient (47 years old) with a mechanical heart valve who was taking warfarin (5 mg/day for 5 years), the International Normalized Ratio (INR) value was decreased from 3.1 to 1.5 after taking Ginsana capsules three times a day for two weeks for rejuvenation. It has been reported that it recovered to 3.3 after stopping ginseng intake [82]. However, the exact causal relationship was not clear because he simultaneously consumed diltiazem hydrochloride and nitroglycerin, which are vasodilators, and salsalate, an anti-inflammatory drug. If the INR level is low, blood coagulation occurs easily, and if the INR level is high, there is a risk of bleeding, so it needs to be adjusted to an appropriate level. Jiang and co-workers conducted a clinical evaluation of 12 male subjects. Korean ginseng (3 g/day) was administered for one week, and the antithrombotic drug warfarin (25 mg) was administered once before and after administration. Changes in S-warfarin (S-7-hydroxy -warfarin), which is metabolized by CYP2C9 enzyme in the blood, and R-warfarin, by CYP3A4 and CYP2C9 enzymes, were analyzed to test the effect of combined ginseng on warfarin metabolism. As a result, ginseng administration did not affect pharmacokinetic indicators such as excretion or distribution of warfarin metabolites or changes in blood coagulation (INR) and platelet aggregation ability in healthy subjects [83]. Warfarin, Korean red ginseng (1 g/day) and placebo were administered in combination and changes of warfarin concentration and INR were examined in blood at 3 and 6 weeks after administration. There was no significant difference in INR between the placebo and the red ginseng administration groups [84]. In addition, the possibility of drug interaction between ginseng and warfarin was evaluated in a randomized, open-controlled trial targeting patients with newly diagnosed ischemic stroke (n = 25). The group was divided into a group administered simultaneously with Korean ginseng and warfarin (n = 12) and a group administered alone with warfarin (n = 13), and administered for 2 weeks, and changes in prothrombin time (PT) and INR index were examined. As a result of the examination at 2 and 3 weeks after administration, there was no significant difference between the two groups, indicating that ginseng did not affect the efficacy of warfarin [85]. Based on clinical trial results to date, there is insufficient clinical evidence for the possibility of ginseng interacting with warfarin. However, because the number of subjects in the clinical trial was small and warfarin was taken in healthy people for a short period of time, it may be different for patients taking warfarin (Table 4).

7.3. Interaction with the other drugs

As an example of a possible adverse reaction, an increase in the risk of bleeding was reported when ginseng, known to show an inhibitory effect on platelet aggregation, and aspirin were administered simultaneously [86]. It is recommended that surgical patients stop using ginseng at least 7 days before surgery due to the possibility of causing bleeding [87]. In addition, ginseng has been shown to enhance the efficacy of the vasodilator, nifedipine, or reduce the efficacy of the diuretic furosemide [86]. The several effects of ginseng on opioids have been reported to reduce the analgesic effect of opioids such as morphine, U-50, and 488H in animal test [88]. Meanwhile, Korean ginseng has been found to strengthen the analgesic effects of pentazocine and aspirin [89]. Furthermore, ginseng has been used as a complementary remedy in patients receiving antiretroviral therapy, resulting in elevated plasma concentrations of raltegravir, an antiretroviral medicine, suggesting the association between ginseng and CYP3A4-metabolized drugs [90]. In another mice experiments, ginseng was shown to inhibit the formation of tolerance to opioids and psychostimulants [91]. Animal test results also showed that pain relief caused by morphine was antagonized by total saponin of ginseng and the formation of analgesic tolerance and physical dependence on morphine was also suppressed [92]. The mechanism of drug interaction between ginseng and opioids has been assumed to be involved in non-narcotic analgesic phenomena in the central nervous system, but the exact mechanism is unknown. Therefore, it is noteworthy that the analgesic effect of narcotic opioids may be reduced in patients who consume ginseng [93]. Besides, the blood sugar-lowering effect of ginseng is not significant, but in diabetic patients, the combined drug treatment of ginseng with oral hypoglycemic agents and insulin may cause additive effects and increase the risk of hypoglycemia, so caution is required [94,95]. When midazolam, a sleeping drug, and fexofenadine, an antihistamine drug, were coadministered with Korean red ginseng, drug interactions were examined

Table 4
Clinical trials and case reports of ginseng-drug interactions.

Study design	Ginseng types/Dosage	Interacting drugs	Interaction	Reference
Chronic myelogenous lukemia patient (Case report)	Daily ingestion of ginseng energy drinks for 3 months	Imatinib (400 mg/day, 7 years)	Induction of hepatotoxicity from patients	[76]
47-year-old man with St. Jude type mechanical heart value (Case report)	Ginseng capsules (Ginsana) 3 times daily	Warfarin (5 mg/day) (Diltiazem, NTG, Salsalate)	International Normalized Ratio (INR)↓: 3.1 → 1.5	[82]
Healthy volunteers (n = 12) (20–40 years) (Open-label, three way crossover randomized study)	Ginseng (3 g/day, 7 days)	Warfarin (25 mg, single dose)	No significant differences in the pharmacokinetics and pharmacodynamics	[83]
Cardiac valve replacement patients (n = 25) (Randomized control study)	Ginseng (1 g/day, 41 days)	Warfarin (40.60 ± 14.53 mg/week) Duration of therapy: 17.10 ± 9.57 years	No significant differences in mean INR changes	[84]
Patients newly diagnosed with ischemic stroke (n = 25) (Randomized control study)	Ginseng (1.5 g/day, 14 days)	Warfarin (2 mg/day for the first 7 days and 5 mg/day for the next 7 days)	No significant differences in peak values and INR, and also prothrombin time	[85]
HIV+, long-term hepatitis C patients (Case report)	Ginseng tablet (1 g/day, 39 days)	Raltegravir (lopinavir 400/100 mg twice daily, aspirin 100 mg daily and esomeprazole 40 mg daily)	Acute elevation of liver enzymes, marked jaundice and significant weight loss, plasma concentration of raltegravir ↑	[90]

↑: upregulation, ↓: downregulation.

through the drug-metabolizing enzymes CYP and Pgp transporter. It was suggested that Korean red ginseng reduces exposure to fexofenadine in a dose-dependent manner, necessitating a cautious approach when used in combination with Pgp substrate drugs [96]. The interaction between valsartan, an angiotensin II receptor antagonist, known as a substrate of the organic anion transporting polypeptide (OATP) transporter and Korean red ginseng has been recently studied. Neither red ginseng extract nor G-Rc changed the pharmacokinetics of valsartan when red ginseng orally administered to rats. Therefore, the slight interaction between valsartan and Korean red ginseng will provide clinically useful information for taking antihypertensive drugs, antidiabetic drugs or anticancer drugs [97].

8. Conclusions and perspectives

Research on the pharmacokinetic (PK) properties of ginsenosides is helpful in clinically understanding the mechanism of action and safety of ginseng. In order to identify the ADME (Absorption, Distribution, Metabolism and Exccretion) characteristics of ginseng, it is necessary to focus on studying the biotransformation of ginsenosides and the metabolizing transformation of various metabolites in the gastrointestinal tract, intestine and liver. And also, further pharmacokinetic studies on ginseng are needed to extensively study naturally existing ginsenosides and their metabolites based on pharmacokinetic properties such as drug metabolizing enzyme and drug transporter in the intestine and liver as well as drug interactions. Recently, with the rapid development of various hyphenated chromatography-mass spectrometry (HPLC-MS/MS, GC-MS/MS etc.), it is expected that there will be no difficulty in

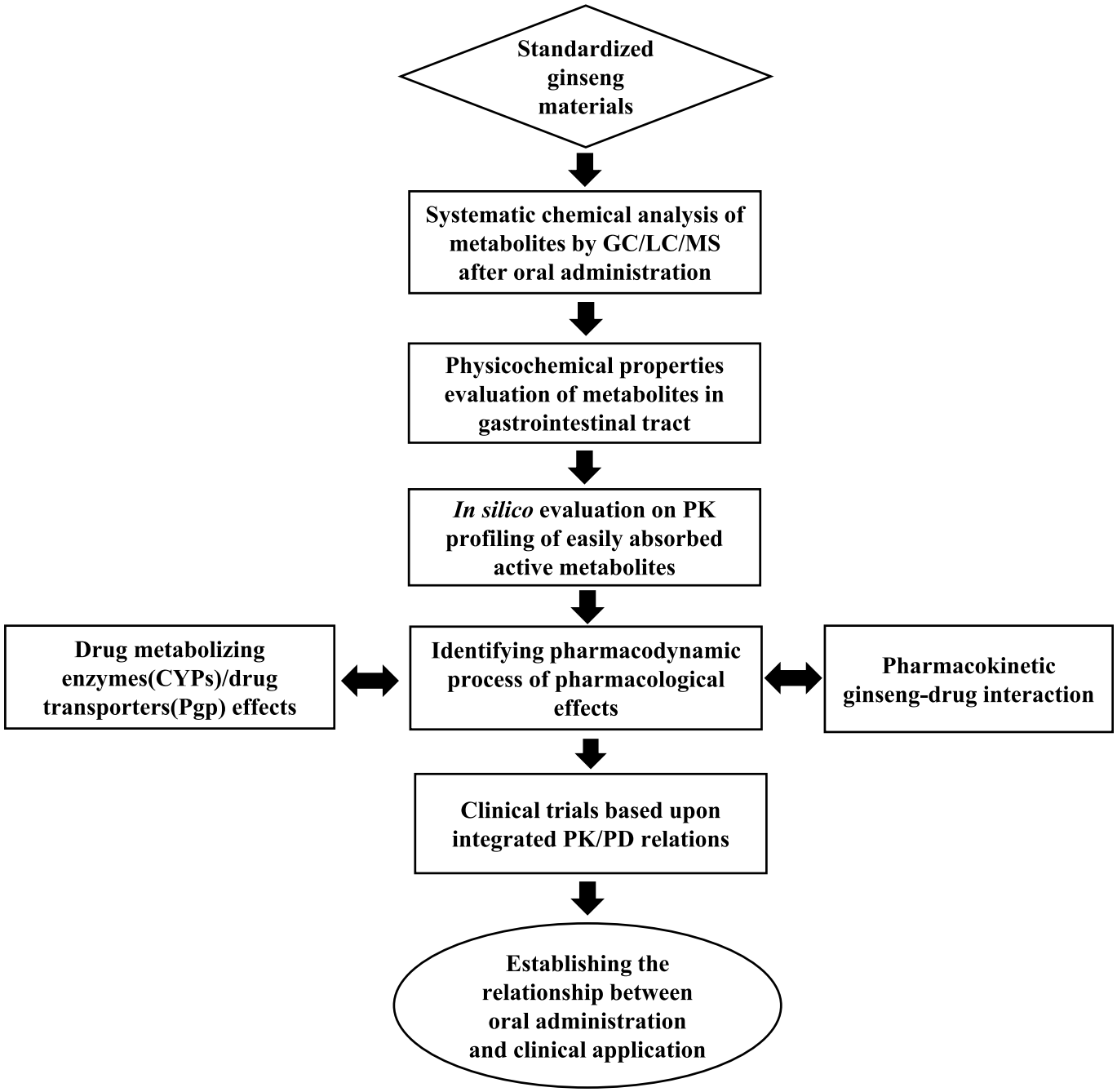

Fig. 6. The proposed strategy and future perspective for integrated pharmacokinetic study of ginseng. PK: pharmacokinetic, PD: pharmacodynamic.

determining the PK profiles of major metabolites. This PK profile will provide clues to the true effects of ginseng and the possible effects of ginsenoside metabolites, and also their target tissues or organs. However, since they are diverse and complicated, an integrated PK study related to the pharmacological effects is required in the future.

Accordingly, the author would like to suggest several directions for further metabolic research of ginseng based upon PK properties of ginsenosides. First, it is necessary to analyze as much as possible about kinds and content of numerous ginsenoside metabolites using high resolution LC/MS/MS, GC/MS/MS and so on. Second, it is necessary to evaluate the physicochemical properties of ginsenoside metabolites for permeability to the biological barrier and ease of absorption into the blood. Third, PK profiling of easily absorbed active ginsenosides needs to be confirmed through *in silico* evaluation, meaning that the number of potential active metabolites could be minimized. Fourth, because the active ginsenosides must show a pharmacodynamic process of pharmacological effect after oral administration, the pharmcokinetic and pharmcodynamic relationships needs to be reasonably presented at various dosage levels. Fifth, it is necessary to conduct experimental studies on ginseng and drug interactions for the safety and the possible mechanism of clinical application. Lastly, it is believed that the clinical PK profile of favorable active ginsenosides can predict substantial pharmacological effects and also promising time window or target tissue in the human body (Fig. 6).

In conclusion, it is difficult to clinically apply these research results so far because ginseng has various active components, origins and formulations. In the future, only clinical studies of pharmacokinetic-pharmacodynamic correlation conducted with standardized ginseng materials will be able to provide reproducible and reliable clinical confirmation, thereby establishing and better understanding the safety of taking ginseng and optimal clinical application.

Declaration of competing interest

The author declares no conflict of interest.

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References

[1] Kobashi K. Glycosides are natural prodrugs: evidence using germfree and gnotobiotic rats associated with a human intestinal bacterium. J Tradit Med 1998;15:1–13.
[2] Park JD. Recent studies on the chemical constituents of Korean ginseng(*Panax ginseng* C. A. Meyer). J Ginseng Res 1996;20:389–415.
[3] Yang L, Liu Y, Liu CX. Metabolism and pharmacokinetics of ginsenosides. Asian Journal of Pharmacodynamics and Pharmacokinetics 2006;6:103–20.
[4] Cho HJ, Yoon IS. Pharmacokinetic interactions of herbs with cytochrome p450 and p-glycoprotein. Evid Based Complement Alternat Med 2015;2015:1–10.
[5] Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. Lance 2007;370:185–91. 2007.
[6] Nam KY, Yang BW, Shin WS, Park JD. A systematic review on potential drug interactions of Korean ginseng based upon cytochrome P450 and P-glycoprotein. Korean J Pharmacogn 2018;49:85–102.
[7] Karikura M, Miyase T, Tanizawa H, Taniyama T, Takino Y. Studies on absorption, distribution, excretion and metabolism of ginseng saponins. VI. The decomposition products of ginsenoside Rb2 in the stomach of rats. Chem Pharm Bull 1991;39:400–4.
[8] Karikura M, Miyase T, Tanizawa H, Taniyama T, Takino Y. Studies on absorption, distribution, excretion and metabolism of ginseng saponins. VII. Comparison of the decomposition modes of ginsenosides Rb1 and Rb2 in the digestive gtract of rats. Chem Pharm Bull 1991;39:2357–61.
[9] Bae EA, Han MJ, Kim EJ, Kim DH. Transformation of ginseng saponins to ginsenoside Rh2 by acids and human intestinal bacteria and biological activities of their transformants. Arch Pharm Res (Seoul) 2004;27:61–7.
[10] Takino Y. Studies on the pharmacodynamics of ginsenoside Rg1, Rb1 and Rb2 in rats. Yakugaku Zasshi 1994;114:550–64.
[11] Huang J, Gong MJ, Bai JQ, Su H, Gong L, Huang ZH, Qiu XH, Xu W, Zhang J. Differential metabolic profiles of ginsenosides in artificial gastric juice using ultra-high-pressure liquid chromatography coupled with linear ion trap-orbitrap mass spectrometry. Biomed Chromatogr 2022;36:e5493.
[12] Nicholson JK, Holmes E, Wilson ID. Gut microorganisms, mammalian metabolism and personalized health care. Nat Rev Microbial 2005;3:431–8.
[13] Hasegawa H, Sung JH, Benno Y. Role of human intestinal Prevotella oris in hydrolyzing ginseng saponin. Planta Med 1997;63:436–40.
[14] Bae EA, Park SY, Kim DH. Constitutive β-glucosidases hydrolysing ginsenoside Rb1 and Rb2 from human intestinal bacteria. Biol Pharm Bull 2000;23:1481–5.
[15] Lee DS, Kim YS, Ko CN, Cho KH, Bae HS, Lee KS, Kim JJ, Park EK, Kim DH. Fecal metabolic activities of herbal components to bioactive compounds. Arch Pharm Res (Seoul) 2022;25:165–9.
[16] Karikura M, Miyase T, Tanizawa H, Takino Y, Taniyama T, Hayashi T. Studies on absorption, distribution, excretion and metabolism of ginseng saponin. V. The decomposition products of ginsenoside Rb2 in the large intestine of rats. Chem Pharm Bull 1990;38:2859–61.
[17] Karikura M, Miyase T, Tanizawa H, Taniyama T, Takino Y. Studies on absorption, distribution, excretion and metabolism of ginseng saponin. VII. Comparison of rhe decomposition modes of ginsenosides Rb1 and Rb2 in the digestive tract of rats. Chem Pharm Bull 1991;39:2357–61.
[18] Bae EA, Choo MK, Park EK, Park SY, Shin HY, Kim DH. Metabolism of ginsenoside Rc by human intestinal bacteria and its related antiallergic activity. Biol Pharm Bull 2002;25:743–7.
[19] Wang Y, Liu TH, Wang W, Wang BX. Research on the transformation of ginsenoside Rg1 by intestinal flora. Zhongguo Zhongyao Zazhi 2001;26:188–90.
[20] Bae EA, Han MJ, Choo MK, Park SY, Kim DH. Metabolism of 20(S)- and 20(R)-ginsenoside Rg3 by human intestinal bacteria and its relation to in vitro biological activities. Biol Pharm Bull 2002;25:58–63.
[21] Hasegawa H. Proof of the mysterious efficacy of ginseng : basic and clinical trials : metabolic activation of ginsenoside : deglycosylation by intestinal bacteria and esterification with fatty acid. J Pharmacol Sci 2004;95:153–7.
[22] Jeon JH, Park JH, Jeon SY, Pang M, Choi MK, Song IS. Concomitent administration of red ginseng extract with lactic acid bacteria increasess the plasma concentration of deglycosylated ginsenosides in healthy human subjects. Biomolecules 2022;12:1896. https://doi.org/10.3390/biom12121896.
[23] Kim DH. Gut microbiota-mediated pharmacokinetics of ginseng saponins. J Ginseng Res 2018;42:255–63.
[24] Kanaoka M, Kato H, Shimada F, Yano S. Studies on the enzyme immuno-assay of bioactive constituents in oriental medicinal drugs VII : enzyme immuno-assay of ginsenoside Rb1 from *Panax ginseng*. Chem Pharm Bull 1992;40:314–7.
[25] Akao T, Kida H, Kanaok M, Hattori M, Kobashi M. Intestinal bacterial hydrolysis is required for the appearance of compound K in rat plasma after oral administration of ginsenoside Rb1 from *Panax ginseng*. J Pharm Pharmacol 1998;50:1155–60.
[26] Paek IB, Moon Y, Kim J, Ji HY, Kim SA, Sohn DH, Kim JB, Lee HS. Pharmacokinetics of a ginseng saponin metabolite compound K in rats. Biopharm Drug Dispos 2006;27:39–45.
[27] Xu QF, Fang XL, Chen DF. Pharmacokinetics and bioavailability of ginsenoside Rb1 and Rg1 from *Panax notoginseng* in rats. J Ethnopharmacol 2003;84:187–92.
[28] Qian T, Cai Z, Wong RN, Mak NK, Jiang ZH. In vivo rat metabolism and pharmacokinetic studies of ginsenoside Rg3. J Chromatogr, B: Anal Technol Biomed Life Sci 2005;816:223–32.
[29] Pang H, Wang HL, Fu L, Sui CY. Pharmacokinetic studies of 20(R)-ginsenoside Rg3 in human volunteers. Yao Xue Xue Bao 2001;36:170–3.
[30] Kim EO, Cha KH, Lee EH, Kim SM, Choi SW, Pan CH, Um BH. Bioavailability of ginsenosides from white and red ginsengs in the simulated digestion model. J Agric Food Chem 2014;62:10055–63.
[31] Pan W, Xue B, Yang C, Miao L, Zhou L, Chen Q, Cai Q, Liu Y, Liu D, He H, Zhang Y, Yin T, Tang X. Biopharmaceutical characters and bioavailability improving strategies of ginsenosides. Fitoterapia 2018;129:272–82.
[32] Wang M, Li H, Liu W, Cao H, Hu X, Gao X, Xu F, Li Z, Hua H, Li D. Dammaran-type leads panaxadiol and protopanaxadiol for drug discovery: biological activity and structural modification. Eur J Med Chem 2020;189:112087.
[33] Paek IB, Moon Y, Kim J, Ji HY, Kin SA, Sohn DH, Kim JB, Lee HS. Pharmacokinetics of a ginseng saponion metabolite compound K in rats. Biopharm Drug Dispos 2006;27:39–45.
[34] Hasegawa H, Sung JH, Matsumiya S, Uchiyama M. Main ginseng saponin metabolites formed by intestinal bacteria. Planta Med 1996;62:453–7.
[35] Wakabayashi G, Hasegawa H, Murata J, Saiki I. In vivo antimetastatic action of ginseng protopanaxadiol saponins is based on their intestinal metabolites after oral administration. Oncol Res 1997;9:411–7.
[36] Tawab MA, Bahr U, Karas M, Wurglics M, Schbert-Zsilavecz M. Degradation of gisenosides in human after oral administration. Drug Metab Dispos 2003;31:1065–71.
[37] Ryu JS, Lee HJ, Bae SH, Kim SY, Park Y, Suh HJ, Jeong YH. The bioavailability of red ginseng extract fermented by *Phellinus Linteus*. J Ginseng Res 2013;37:108–16.
[38] Kim HK. Pharmacokinetics of ginsenoside Rb1 and its metabolite compound K after oral administration of Korean red ginseng extract. J Ginseng Res 2013;37:451–6.
[39] Fukami H, Ueda T, Matsuoka N. Pharmacokinetic study of compound K in Japanese subjects after ingestion of *Panax ginseng* fermented by *Lactobacillus paracasei A221* reveals significant increase of absorption into blood. J Med Food 2018. https://doi.org/10.1089/jmf.2018.4271.
[40] Chen Z, Zhang Z, Liu J, Qi H, Li J, Chen J, Huang Q, Liu Q, Mi Q, Li X. Gut microbiota: therapeutic targets of ginseng against multiple disorders and ginsenoside transformation. Front Cell Infect Microbiol 2022;12:853981.
[41] Hasegawa H, Lee KS, Nagoka T, Tezuka Y, Uchiyama M, Kadota S, Saiki I. Pharmacokinetics of ginsenoside deglycosylation by intestinal bacteria and its

transformation to biologically active fatty acid esters. Biol Pharm Bull 2000;23:298–304.
[42] Hasegawa H, Suzuki R, Nagoka T, Tezuka Y, Kadota S, Saiki I. Prevention of growth and metastasis of murine melanoma through enhanced natural killer cytotoxicity by fatty acid conjugate of protopnaxatriol. Biol Pharm Bull 2002;25:861–6.
[43] Hao H, Lai L, Zheng C, Wang Q, Yu G, Zhou X, Wu L, Gong P, Wang G. Microsomal cytochrome P450-mediated metabolism of protopanaxadiol ginsenosides: metabolic profile, reaction phenotyping, and structure-metabolism relationship. Drug Metabol Dispos 2010;38:1731–9.
[44] Ma LY, Zhou QL, Yang XB, Wang HP, Yang XW. Metabolism of 20(S)-ginsenoside Rg2 by rat liver microsomes: bioactivation to SIRT1-activating metabolites. Molecules 2016;21:757. https://doi.org/10.3390/molecules21060757.
[45] Tanizawa H, Karikuma M, Miyase T, Takino Y. Studies on the metabolism and decomposition and distribution of ginsenoside Rb2 in rats. Proc 6th Int Ginseng Symp 1993:187–94.
[46] Kim SW, Han BC, So SH, Han CK, In G, Park CK, Hyun SH. Biodistribution and pharmacokinetic evaluation of Koran red ginseng components using radioisotopes in a rat model. J Ginseng Res 2023;47:74–80.
[47] Ban MS, Kim Y, Lee S, Han BY, Yu KS, Jang IJ, Chung HK, Lee SH. Pharmacokinetics of ginsenoside compound K from a compound K fermentation product, CK-30, and from red ginseng extract in healthy Korean subjects. Clinical Pharmacology in Drug Development 2021;00:1–7.
[48] Sharma A, Lee HJ. Ginsenoside compound K: insights into recent studies on pharmacokinetics and health-promoting activities. Biomolecules 2020;10:1028. https://doi.org/10.3390/biom10071028.
[49] Chen J, Li M, Chen L, Wang Y, Li S, Zhang Y, Zhang L, Song M, Liu C, Hua M, Sun Y. Effects of processing method on the pharmacokinetics and tissue distribution of orally administered ginseng. J Ginseng Res 2018;42:27–34.
[50] Kim JK, Choi MS, Jeung W, Ra J, Yoo HH, Kim DH. Effects of gut microbiota on the pharmacokinetics of protopanxadiol ginsenosides Rd, Rg3, F2 and compound K in healthy volunteers treated orally with red ginseng. J Ginseng Res 2020;44:611–8.
[51] Won HJ, Kim HI, Park T, Kim H, Jo K, Jeon H, Ha SJ, Hyun JM, Jeong A, Kim JS, Park YJ, Eo YH, Lee J. Non-clinical pharmacokinetic behavior of ginsenosides. J Ginseng Res 2019;43:354–60.
[52] Miao L, Yang Y, Li Z, Fang Z, Zhang Y, Han C. Ginsenoside Rb2: a review of pharmacokinetics and pharmacological effects. J Ginseng Res 2022;46:206–13.
[53] Kim HJ, Oh TK, Kim YH, Lee J, Moon JM, Park YS, Sung CM. Pharmacokinetics of ginsenoside Rb1, Rg3, Rk1, Rg5, F2, and compound K from red ginseng extract in healthy Korean volunteers. Evid Based Complement Alternat Med 2022;Jan;24:8427519. https://doi.org/10.1155/2022/8427519. 2022.
[54] Guengerich FP. Cytochrome P-450 3A4 : regulation and role in drug metabolism. Annu Rev Pharmacol Toxicol 1999;39:1–17.
[55] Liu Y, Zhang JW, Li W, Ma H, Sun J, Deng MC, Yang L. Ginsenoside metabolites, rather than naturally occurring ginsenosides, lead to inhibition of human cytochrome P450 enzymes. Toxicol Sci 2006;91:356–64.
[56] Liu Y, Li W, Li P, Deng MC, Yang SL, Yang L. The inhibitory effect of intestinal bacterial metabolite of ginsenosides on CYP3A activity. Biol Pharm Bull 2004;27:1555–60.
[57] Xiao J, Chen D, Lin XX, Peng SF, Xiao MF, Huang WH, Wang YC, Peng JB, Zhang W, Ouyang DS, Chen Y. Screening of drug metabolizing enzymes for the ginsenoside compound K in vitro : an efficient anticancer substance originating from Panax ginseng. PLoS One 2016;11:e0147183.
[58] Chiu N, Tomlinson Guns ES, Adomat H, Jia W, Deb S. Idntification of human cytochrome P450 enzymes involved in the hepatic and intestinal biotransformation of 20(S)-protopanaxadiol. Biopharm Drug Dispos 2014;35:104–18.
[59] Deb S, Chin M, Adomat H, Guns ES. Ginsenoside-mediated blockade of 1α, 25-dihydroxyvitamin D3 inactivation in human liver and intestine in vitro. J Steroid Biochem Mol Biol 2014;141:94–103.
[60] Hao M, Zhao Y, Chen P, Huang H, Liu H, Jiang H, Zhang R, Wang H. Structure-activity relationship and substrate-dependent phenomena in effects of ginsenosides on activities of drug-metabolizing P450 enzymes. PLoS One 2008;3:e2697.
[61] Hao M, Ba Q, Yin J, Li J, Zhao Y, Wang H. Deglycosylated ginsenosides are more potent inducers of CYP1A1, CYP1A2 and CYP3A4 expression in HepG2 cells than glycosylated ginsenosides. Drug Metabol Pharmacokinet 2011;26:201–5.
[62] Lee SG, Cho KH, Nguyen TTL, Vo DK, Chae YJ, Maeng HJ. Inhibitory effect of 20(S)-protopanaxadiol on cytochrome P450: potential of its pharmacokinetic interactions in vivo. Biomed Pharmacother 2022;153:113514.
[63] Balayssac D, Authier N, Cayre A, Coudore F. Does inhibition of P-glycoprotein lead to drug-drug interactions. Toxicol Lett 2005;156:319–29.
[64] Liang Y, Zhou Y, Zhang J, Rao T, Zhou L, Xing R, Wang Q, Fu H, Hao K, Xie L, Wang G. Pharmacokinetic compatibility of ginsenosides and Schisandra Lignans in Shengmai-san: from the perspective of p-glycoprotein. PLoS One 2014;9:e98717.
[65] Zhang J, Zhou F, Niu F, Wu X, Sun J, Wang G. 20(S)-ginsenoside Rh2 noncompetitively inhibits P-glycoprotein in vitro and in vivo : a case for herb-drug interactions. Drug Metabol Dispos 2010;38:2179–87.
[66] Yang LQ, Wang B, Gan H, Fu ST, Zhu XX, Wu ZN, Zhan DW, Gu RL, Dou GF, Meng ZY. Enhanced oral bioavailability and antitumor effect of paclitaxel by 20(S)-ginsenoside Rg3 in vivo. Biopharmaceuticals and Drug Position 2012;33:425–36.
[67] Yang Z, Wang JR, Niu T, Gao S, Yin T, You M, Jiang ZH, Hu M. Inhibition of P-glycoprotein of compound K, an anticancer metabolite of red ginseng extract produced by gut microflora. Drug Metabol Dispos 2012;40:1538–44.
[68] Li N, Wang D, Ge G, Wang X, Liu Y, Yang L. Ginsenoside metabolites inhibit P-glycoprotein in vivo and in situ using three absorption models. Planta Med 2014;80:290–6.
[69] Xiong J, Yuan H, Fei S, Yang S, You M, Liu L. The preventive role of the red ginseng ginsenoside Rg3 in the treatment of lung tumorigenesis induced by benzo(a) pyrene. Sci Rep 2023;13:4528.
[70] Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, Cui Y, Ang CY. Cytochrome P450 phenotypic ratios for predicting herb-drug interactions in humans. Clin Pharmacol Therapeut 2002;72:276–87.
[71] Anderson GD, Rosito G, Mohustsy MA, Elmer GW. Drug interaction potential of soy extract and Panax ginseng. J Clin Pharmacol 2003;43:643–8.
[72] Malati CY, Robertson SM, Hunt JD, Chairez C, Alfaro RM, Kovacs JA, Penzak SR. Influence of Panax ginseng on cytochrome P450 (CYP)3A and P-glycoprotein (P-gp) activity in healthy participants. J Clin Pharmacol 2012;52:932–9.
[73] Kim DS, Kim Y, Jeon JY, Kim MG. Effect of Red Ginseng on cytochrome P450 and P-g lycoprotein activities in healthy volunteers. J Ginseng Res 2016;40:375–81.
[74] Kim MG, Kim Y, Jeon JY, Kim DS. Effect of fermented red ginseng on cytochrome P450 and P-glycoprotein activity in healthy subjects, as evaluated using the cocktail approach. Br J Clin Pharmacol 2016;82:1580–90.
[75] Park JD. Antitumor activities of Korean ginseng as a health food based upon underlying mechanisms of ginsenosides. In: Chemistry of koran foods and beverages, ACS symposium series. Washington, DC: American Chemical Society; 2019. p. 149–68.
[76] Bilgi N, Bell K, Ananthakrishnan AN, Atallah E. Imatinib and Panax ginseng: a potential interaction resulting in liver toxicity. Ann Pharmacother 2010;44:926–8.
[77] Collado-Borrell R, Escudero-Vilaplana V, Romero-Jimenez R, Iglesias-Peinado I, Herranz-Alonso A, Sanjurjo-Saez M. Oral antineoplastic agent interactions with medicinal plants and food: an issue to take into account. J Cancer Res Clin Oncol 2016;142:2319–30.
[78] Park J, Song H, Kim SK, Lee MS, Rhee DK, Lee Y. Effects of ginseng on two main sex steroid hormone receptors: estrogen and androgen receptors. J Ginseng Res 2017;41:215–21.
[79] King ML, Adle SR, Murphy LL. Extraction-dependent effects of American ginseng (Panax quinquefolium) on human breast cancer cell proliferation and estrogen receptor activation. Integr Cancer Ther 2006;5:236–43.
[80] Hsu WL, Tsai YT, Wu CT, Lai JN. The prescription pattern of Chinese herbal products containing ginseng among tamoxifen-treated female breast cancer survivors in Taiwan: a population-based study. Evid Based Complement Alternat Med 2015:385204.
[81] Cui Y, Shu XO, Ga YT, Cai H, Tao MH, Zheng W. Association of ginseng use with survival and quality of life among breast cancer patients. Am J Epidemiol 2006;163:645–53.
[82] Janetzky K, Morreale AP. Probable interaction between warfarin and ginseng. Am J Health Syst Pharm : AJHP : Official Journal of the American Society of Health-System Pharmacists 1997;54:692–3.
[83] Jiang X, Williams KM, Liauw WS, Ammit AJ, Roufogalis BD, Duke CC, Day RO, McLachlan AJ. Effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Clin Pharmacol 2004;57:592–9.
[84] Lee YH, Lee BK, Choi YJ, Yoon IK, Chang BC, Gwak HS. Interaction between warfarin and Korean red ginseng in patients with cardiac valve replacement. Int J Cardiol 2010;145:275–6.
[85] Lee SH, Ahn YM, Ahn SY, Doo HK, Lee BC. Interaction between warfarin and Panax ginseng in ischemic stroke patients. J Alternative Compl Med 2008;14:715–21. 2008.
[86] Elmer GW, Lafferty WE, Tyree PT, Lind BK. Potential interactions between complementary/alternative products and conventional medicines in a Medicare population. Ann Pharmacother 2007;41:1617–24.
[87] Ang-Lee MK, Moss J, Yuan CS. Herbal medicines and perioperative care. JAMA 2001;286:208–16.
[88] Takahashi M, Tokuyama S. Pharmacological and physiological effects of ginseng on actions induced by opioids and psychostimulants. Methods Find Exp Clin Pharmacol 1998;20:77–84.
[89] Mitra SK, Chakraborti A, Bhattacharya SK. Neuropharmacological studies on Panax ginseng. Indian J Exp Biol 1996;34:41–7.
[90] Mateo-Carrasco H, Galvez-Contrertas MC, Fernandez-Gines FD, Nguyen TV. Elevated liver enzymes resulting from interaction between Raltegravir and Panax ginseng : a case report and brief review. Drug Metabol Drug Interact 2012;27:171–5.
[91] Bhargava HN, Ramarao P. The effect of Panax ginseng on the development of tolerance to the pharmacological actions of morphine in the rat. Gen Pharmacol 1991;22:521–5.
[92] Kim HC, Shin EJ, Jang CG, Lee MK, Eun JS, Hong JT, Oh KW. Pharmacological action of Panax ginseng on the behavioral toxicities induced by psychotropic agents. Arch Pharm Res (Seoul) 2005;28:995–1001.
[93] Abebe W. Herbal medication: potential for adverse interactions with analgesic drugs. J Clin Pharm Therapeut 2002;27:391–401.
[94] Kiefer D, Pantuso T. Panax ginseng. Am Fam Physician 2003;68:1539–42.
[95] Seo SH, Park GK, Park JD. Korean ginseng and diabetes: an insight into antidiabetic effects of Korean ginseng(*Panax ginseng* C. A. Meyer) in cultured cells, animal models and human studies. Korean J Pharmacogn 2020;51:1–29.
[96] Kim SJ, Choi S, Kim M, Park C, Kim GL, Lee SO, Kang W, Rhee DK. Effect of Korean red ginseng extracts on drug-drug interaction. J Ginseng Res 2018;42:370–8.
[97] Jeon JH, Lee S, Lee W, Jin S, Kwon M, Shin CH, Choi MK, Song IS. Herb-drug interaction of red ginseng extract and ginsenoside Rc with valsartan in rats. Molecules 2020;25:622. https://doi.org/10.3390/molecules25030622.