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The Possible Role of Intestinal Microflora in Pharmacological Activities of Ginseng

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ABSTRACT

Ginseng, which contains protopanaxadiol and protopanaxatriol ginsenosides as major constituents, has been used as a herbal medicine for more than 2000 years. When ginseng is orally administered to humans or experimental animals, its protopanxadiol ginsenosides are transformed predominantly to compound K by intestinal bacteria, and its protopanaxatriol ginsenosides are transformed to ginsenoside Rh1, ginsenoside F1, and protopanaxatriol by gastric juices and intestinal microflora. The fecal compound K-forming activity profile of ginseng extract in ginseng-treated individuals is proportional to that of the area under the blood concentration curve for compound K. Furthermore, compound K, ginsenoside Rh1 and protopanaxadiol may be absorbed into blood. These metabolites exhibit more potent pharmacological effects, such as, anti-tumor, anti-inflammatory, anti-diabetic, anti-allergic and neuroprotective effects, than the parental ginsenosides, such as ginsenoside Rb1, Rb2 or Re, according to *in vitro* studies, parentally administered ginsenosides and their metabolites exhibit these biological effects *in vivo*. Based on these findings, intestinal microflora probably play an important role in the pharmacological action of orally administered ginseng.

Keywords: ginseng, ginsenoside, intestinal microflora, metabolism, fermentation
Abbreviations: ADME, absorption, distribution, metabolism and excretion; **AP**, activator protein-1; **AUC**, area under the blood concentration curve; **COX**, cycoloxygenase; **iNOS**, inducible nitric oxide synthase; **JNK**, c-Jun N-terminal kinases; **LPS**, lipopolysaccharide; **MAPK**, Mitogen-activated protein kinases; **NF-κB**, nucleus factor kappaB; **NO**, nitric oxide; **PGE2**, prostaglandin E2

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INTRODUCTION

The term ginseng is used to refer to the dried roots of several plants of the species *Panax* sp. (Family Araliaceae). The three major commercial ginsengs are *Panax ginseng* CA Meyer (Korean ginseng or Asian Ginseng), which has been used as a herbal medicine for more than 2000 years (Li and Li 1973), *Panax quiquifolium* (North American Ginseng), and *Panax notoginseng* (Chinese Ginseng) (Attle *et al*. 1999; Kennedy and Scholey 2003). Of these, *Panax ginseng* is the most commonly used as an adaptogenic agent, and has been shown to enhance physical performance, promote vitality, increase resistance to stress and aging, and to have immunomodulatory activity (Singh *et al*. 1984; Scaglione *et al*. 1990).

Many scientists have isolated the bioactive constituents of ginsengs and identified their structures. The structures of these ginsenoside constituents were not established until the 1960's. In 1963, Shibata *et al*. isolated ginseng saponins from *P. ginseng* as major constituents and named them ginsenosides (Shibata *et al*. 1965, 1966). The major saponins were found to be dammarane oligoglycosides, although an oleanane-type was also later identified (Matsuda *et al*. 1986). Furthermore, the dammarane-type saponins are classified into protopanaxadiol- and protopanaxatriol types. For example, raw or dried ginseng contains protopanaxadiols (malonyl-ginsenoside Rb1, malonyl Rb2, malonyl-Rc, malonyl-Rd, ginsenosides Rb1, Rb2, Rc, and others), protopanaxatriols (Re, Rf, Rg1, Rg2, and others), and oleanane (ginsenoside Ro) (Wang *et al*. 1999). However, red ginseng treated with steaming contains ginsenosides Rg3, Rg5, Rk1, Rh2, Rh3, Rk2, Rb1, Rb2, Rc, Re, Rf, Rg1, Rg2, and Ro (Kitagawa *et al*. 1983; Kwon *et al*. 2001).

Today, approximately 200 substances, such as, ginsenosides, polysaccharides, polyacetylenes, peptides, and amino acids, have been isolated from Korean ginseng (Attele *et al*. 1999). Its major components are ginseng saponins (ginsenosides) and polysaccharides. Therefore, to evaluate the pharmacological effects of ginsengs, much research has focused on the ginsenosides.

ABSORPTION, DISTRIBUTION METABOLISM, AND EXCRETION (ADME) OF GINSENG CONSTITUENTS

The pharmacological effects of ginseng, particularly of ginsenosides, may be dependent on the ADME of its constituents. Therefore, to understand the effects of the active compounds in ginseng, pharmacokinetic studies on ginsenosides have been performed in animals and humans. Tawab

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et al. (2003) identified ginsenosides in the plasma and urine samples of two subjects by liquid chromatography-mass/mass (LC–MS/MS), after administering Ginsana extract (ginseng saponin fraction, Pharmaton S.A., Lugano, Switzerland) orally. In both volunteers the same hydrolysis products, which are not originally present in ginseng, were identified in plasma and urine. It was shown that three hydrolysis product types, namely, ginsenoside Rh1 and F1, intestinal metabolites of the protopanaxatriol ginsenosides, and compound K, an intestinal bacterial metabolite of the protopanaxadiol ginsenosides, might reach the systemic circulation. It was suggested that these metabolites (hydrolysates) might be produced from parental ginsenosides in ginseng by intestinal microflora. In addition, ginsenoside Rb1 was detected in the plasma and urine of one subject, but at the lower detection limit. However, Shibata *et al*. could not detect ginsenoside Rb1, though they did detect compound K, in ginseng extract treated subjects. Furthermore, compound K was identified in human serum by specific enzyme immunoassay 8 h after the oral administration of ginseng (Akao *et al*. 1998b). Lee *et al*. (2009) measured ginsenoside Rb1 and compound K levels in the blood of 32 subjects orally treated with white ginseng powder by LC–MS/MS. They also detected compound K in blood, but not ginsenoside Rb1. Subsequently, they estimated C_{max} and T_{max} values and the area under the blood concentration curve (AUC) for compound K in plasma, the values obtained were 27.89 ± 24.46 (ng/ml), 10.76 ± 2.07 h, and 221.98 ± 221.42 (ng* h/ml), respectively. They also suggested that compound K may be a primary intestinal bacterial metabolite of protopanaxadiol ginsenosides in orally treated human subjects.

The metabolites and/or the degradation products identified in plasma and urine probably result from the breakdown of ginsenosides in the gastrointestinal tract by microorganisms, intestinal enzymes, or gastric fluid. To understand the degradation of ginsenosides in the gastrointestinal tract, many experiments have been undertaken using acids, enzymes, intestinal bacteria, and animals (Odani *et al.* 1983; Strombom *et al*. 1985; Karikura *et al*. 1990; Hasegawa *et al*. 1996; Akao *et al*. 1998a).

To examine the transformation of protopanaxadiol glycosides by gastric juice, Karikura *et al*. (1990) and Han *et al*. (1982) investigated the degradation products of ginsenosides under mild acidic conditions. Ginsenoside Rb1 and Rb2 were hydrolyzed to 20(R,S)-ginsenoside Rg3 with dilute HCl, but these ginsenosides were reasonably stable in the rat stomach. Furthermore, metabolites observed in the stomachs of mice differed from the products obtained by HCl hydrolysis. The metabolites of ginsenoside Rb1 in the rat stomach were 25-hydroperoxy-23-ene derivatives, whereas those of ginsenoside Rb2 fell into four types, namely, 25-hydroxyl-23-ene, 24-hydroxy-25-ene, 25-hydroperoxy-23-ene, and 24-hydroperoxy-25-ene derivatives. 20S-protopanaxatriol saponins undergo hydrolysis of the C-20 glycosyl moiety and hydration of the 20S-protopanadiol side chain, whereas 20(S)-protopanaxadiol saponins undergo oxygenation of the protopanaxadiol side chain. Nevertheless, these metabolites were only produced at minor levels in the rat stomach.

Bae *et al.* (2004a) reported that when ginseng power extract was incubated at 60°C under acidic conditions, its protopanaxadiol ginsenosides were transformed to ginsenosides Rg3, Rg5, and Rk1, but that these ginsenosides only slightly hydrolyzed at 37°C. Furthermore, the protopanaxadiol ginsenosides Rb1, Rb2, and Rc isolated from ginseng were only partially transformed to ginsenoside Rg3 by incubation at 60°C under neutral conditions. On the other hand, protopanaxatriol ginsenosides, ginsenoside Rg1 and Re, were easily hydrolyzed to their hydrosates and hydroperoxide derivatives by dilute HCl and in the rat stomach. However, their hydroperoxide derivatives were present only in small quantities. These findings suggest that orally administered protopanaxatriol ginsenosides may be transformed by gastric juice, but that protopanaxadiol ginsenosides are probably resistant.

Therefore, if ginsengs are orally ingested, the majority of hydrophilic ginsenosides inevitably contact intestinal microflora in the alimentary tract, and thus, could be metabolized to deglycosylated hydrophobic metabolites by intestinal microflora (Kobashi and Akao 1997; Kim 2002). These metabolites are then easily absorbed in the gastrointestinal tract, because they are relatively nonpolar as compared with the parental ginsenosides.

For example, when ginseng was orally administered to humans or animals, compound K and ginsenoside Rh1 and F1 were detected in blood as the main components (Akao *et al*. 1998a, 1998b; Shibata *et al*. 2001; Tawab *et al*. 2003). However, ginsenosides Rb1, Rb2, Rc, and Re have not been detected in blood by many researchers (Akao *et al*. 1998a, 1998b; Lee *et al*. 2005), although Tawab *et al*. (2003) detected a small quantity of ginsenoside Rb1, but not of ginsenosides Rb2, Rc, and Re, in blood of one of two subjects. Akao *et al*. (1998a, 1998b) and Lee *et al*. (2005) measured ginsenoside levels in blood and urine in conventional, germ-free, gnotobiotic rats after oral ginsenoside Rb1 administration. Furthermore, compound K was detected among intestinal contents and in the blood and urine of conventional and gnotobiotic rats, but ginsenoside Rb1 was not detected in blood or urine. However, compound K was not detected in the blood or in the intestinal contents of germ-free rats. Kato *et al*. (1990) also investigated ginsenosides in human plasma after the oral administration of red ginseng powder, and although they did not detect ginsenoside Rb1, they detected compound K in blood.

Tawab *et al.* (2003) also reported that ginsenoside Rh1, a protopanaxadiol ginsenoside, was easily detected in blood at 4-5 h and 8-12 h after the oral administration of ginseng, but not at 6-7 h. The first absorption peak may have been due to the hydrolysis of ginsenoside Rg1 by gastric juice and the second peak to intestinal bacterial metabolism with or without degradation by gastric juice. Protopanaxatriol ginsenosides, such as, ginsenosides Re and Rg1, are unstable under acidic conditions. Thus, their C20-sugar is lost when they are exposed to gastric juice. Ginsenosides Rg1 and Re are hydrolyzed to ginsenosides Rh1 and Rg2, respectively, and the hydrosate ginsenoside Rh1 might be absorbed by the stomach and/or small intestine. However, ginsenoside Re hydrosate, ginsenoside Rg2, was not detected in blood, probably because it is not absorbed due to the presence of the terminal rhamnose, like that in quercetin-4-*O*-rhamnoglucoside (Scalbert and Williamson 2000). Therefore, the hydrosate ginsenoside Rg2 and unhydrolyzed ginsenosides Rg1 and Re may be metabolized to ginsenosides Rh1 and/or F1 by intestinal bacteria and then absorbed into blood. Tawab *et al*. also reported that no degradation products of the protopanaxadiol ginsenosides were detected in plasma or urine during in the first few hours after administration, which suggests that the protopanaxadiol ginsenosides are hardly decomposed in the stomach. The prolonged time needed for the appearance of compound K and its hydrated form in plasma indicate that absorption takes place in the lower intestine (**Fig. 1**). However, protopanaxatriols hydrolyzed by gastric juice are absorbed in the stomach and small intestine sooner and protopanaxatriol metabolization by intestinal bacteria occurred in the lower intestine.

Previous *in vitro* experiments have shown that the bacterial intestinal degradation of protopanaxadiol ginsenosides proceeds stepwise *via* the cleavage of sugar moieties, and that this process liberates mainly monoglucosylated ginsenoside compound K (Karikura *et al*. 1990; Hasegawa *et al*. 1996; Bae *et al*. 2002a). Furthermore, when protopanaxadiol ginsenosides were incubated with human intestinal microflora, the main metabolite was found to be compound K (Bae *et al*. 2000, 2003; Kim 2009), and this metabolic pathway was found to be catalyzed by *Bifidobacterium* K-110, *Bifidobacterium* H-1, *Provetella oris*, *Fusobacterium* K-60, *Bacteroides* JY-6, *Eubacterium* A-44, and *Bifidobacterium* K-506 (**Fig. 2**). In addition, the protopanaxadiol ginsenosides are easily transformed to ginseno-

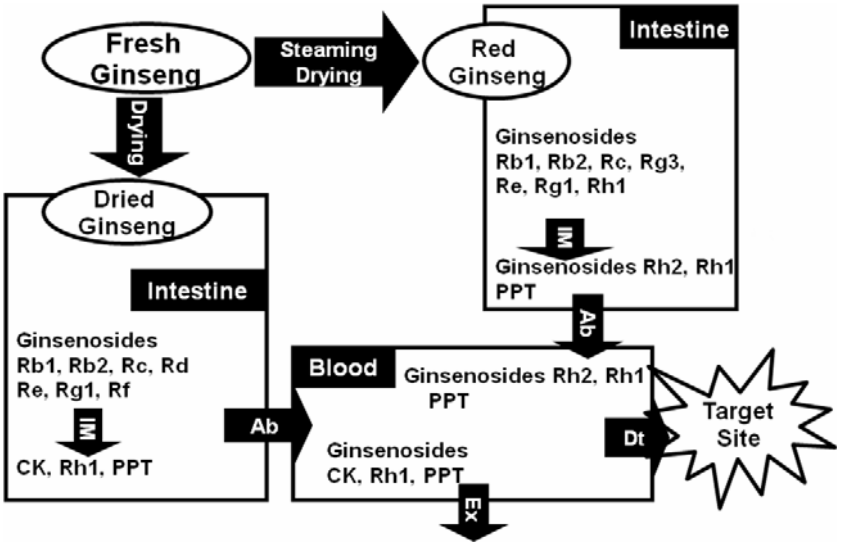

Fig. 1 Proposed fates of the constituents of orally administered ginsengs due to the effects of human intestinal microflora. Ab, absorption; Dt, distribution; Ex, excretion; IM, intestinal microflora.

side Rg3 by mild acids with steaming, and ginsenoside Rg3 is transformed to ginsenoside Rh2 by human intestinal bacteria (Bae *et al*. 2002a). These metabolic pathways are proceeded by β-glucosdiase, α-arabinofuranosidase, and/or α-arabinopyranosidase from *Fusobacterium* K-60 and *Bifidobacterium* K-110 (Shin *et al*. 2003; Bae *et al*. 2005; Park *et al*. 2010). *Bifidobacterium* K-110 is also produced by β-xylosidase, which catalyzes transformations of ginsenosides Ra1 and Ra2 to ginsenosides Rb2 and Rc. These results suggest that protopanaxadiol ginsenosides can be metabolized to compound K in the intestine by intestinal microflora, and to ginsenoside Rh2 by acid and intestinal bacteria.

Protopanaxatriol ginsenosides Re and Rg1 are easily transformed to ginsenoside Rh1 or protopanaxatriol by human intestinal bacteria, and this metabolic pathway is catalyzed by *Fusobacterium* K-60, *Bacteroides* JY-6, *Eubacterium* A-44, and *Bacterodies* HJ-15 (Bae *et al*. 2000, 2005). The most potent ginsenoside Re-metabolizing bacterium, *Bacterioides* JY-6, is an anaerobic, gram-negative, non-spore forming, rod-shaped, α-rhamnosidase-positive, β-glucosidase-positive, and non-gas productive species, which mainly transforms ginsenoside Re to ginsenosides Rh1 and F1, and produces protopanaxatriol as a minor component. Ginsenoside Re is a good substrate for α-L-rhamnosidase from *Bacteroides* JY-6, but this enzyme does not transform ginsenoside Rg1. Similarly, ginsenoside Rg1 is a good substrate for β-glucosidase, but β-glucosidase hydrolyzes ginsenosides Rh1 and F1 only weakly as compared with ginsenoside Rg1. These results suggest that protopanaxatriol ginsenosides may be metabolized to ginsenoside Rh1 or protopanaxatriol by acid or intestinal bacteria.

To investigate whether intestinal bacterial metabolic conversion of ginsenosides to compound K is proportional to the amount compound K in the blood of ginseng-treated volunteers, Lee *et al*. (2009) analyzed the correlation between compound K-forming activity by measuring its levels in the feces of 32 male subjects, and determined the AUC of compound K in plasma. Compound K-forming activities were found to show marked individual differences, and its AUCs were also significantly different in individuals (Lee 2007). Nevertheless, a correlation was found between compound K-forming activity and the AUC of compound K (Spearman's correlation coefficient = 0.402, $P = 0.093$) (**Fig. 3**). In addition, Cui *et al*. (1997) determined total protopanaxatriol and protopanaxadiol ginsenoside amounts as aglycones in the urine samples of subjects orally administered ginseng preparations. It was found that urine levels only accounted for 1.2% of the orally administered dose of protopanaxatriol ginsenosides and considerably smaller amounts of the protopanaxadiol ginsenosides (not exceeding 0.2%). However, Hasegawa *et al*. (2000) reported that intravenously administered compound K selectively accumulated in mouse liver as mono-fatty acid esters, such as, stearyl compound K. Nevertheless, the absorption rates of ginsenosides are low after oral administration, and it has been suggested that this is due to extensive metabolism in the gastrointestinal tract and the poor membrane permeabilities and the low solubilities of deglycosylated ginsenosides.

PHARMACOLOGICAL ACTIVITIES OF GINSENG CONSTITUENTS AND THEIR METABOLITES

It has been reported that ginseng has various pharmacological activities *in vitro* and *in vivo*. Its bioactive constituents are considered ginsenosides, but the pharmacological activities of all constituents of ginseng have not been determined. The ginsenosides have been reported to show antitumor (Wakabayashi *et al*. 1998; Chang *et al*. 2003; Helms 2004), anti-diabetic (Yokozawa *et al*. 1985; Xie *et al*. 2005), anti-inflammatory (Park *et al*. 2004a), and anti-allergic acti--vities (Choo *et al*. 2003; Park *et al*. 2003), to induce endothelium-independent aorta relaxation (Kim *et al*. 1999), and to have adjuvant-like (Wu *et al*. 1992), immunomodulatory (Lee *et al*. 2004), and neuroprotective effects (Park *et al*. 2004b; Shieh *et al*. 2008). These pharmacological effects are dependent on how much of the ginsenosides or of their bioactive metabolites are absorbed into blood. For example, if ginsenoside Rb1 is orally administered to rats, the bioactive ginsenoside absorbed into blood is compound K. Compound K exhibits various pharmacological activities *in vitro*, such as, a cytotoxic effect on tumor cells (Shibata *et al*. 2001; Shin *et al*. 2003a), whereas ginsenosides Rb1 and Rb2 barely exhibit any cytotoxic effect on tumor cells *in vitro*. Of the many ginsenosides, compound K has the greatest cytotoxic effect on tumor cells, followed by ginsenosides Rh2, Rg3, and Rb1 ≅ Rb2. Furthermore, many ginsenosides, including ginsenosides Rb1 and Rb2, and their metabolites have anti-tumor activity *in vitro* (Nakata *et al*. 1998; Choo *et al*. 2008). When the anti-allergic activities of ginsenosides were evaluated *in vitro*, ginsenosides Rh1 and Rh2, and compound K were found to have potent inhibitory effects (Choo *et al*. 2003; Shin *et al*. 2005a). Moreover, these ginsenosides have antiallergic effects *in vivo*. Based on these results, the pharmacological effects of ginseng, particularly ginsenosides, may be dependent on the productions of their bioactive metabolites, such as, compound K, ginsenosides Rh2 and Rh1, and protopanaxatriol, by intestinal microflora.

Compound K Compound K dramatically suppresses the

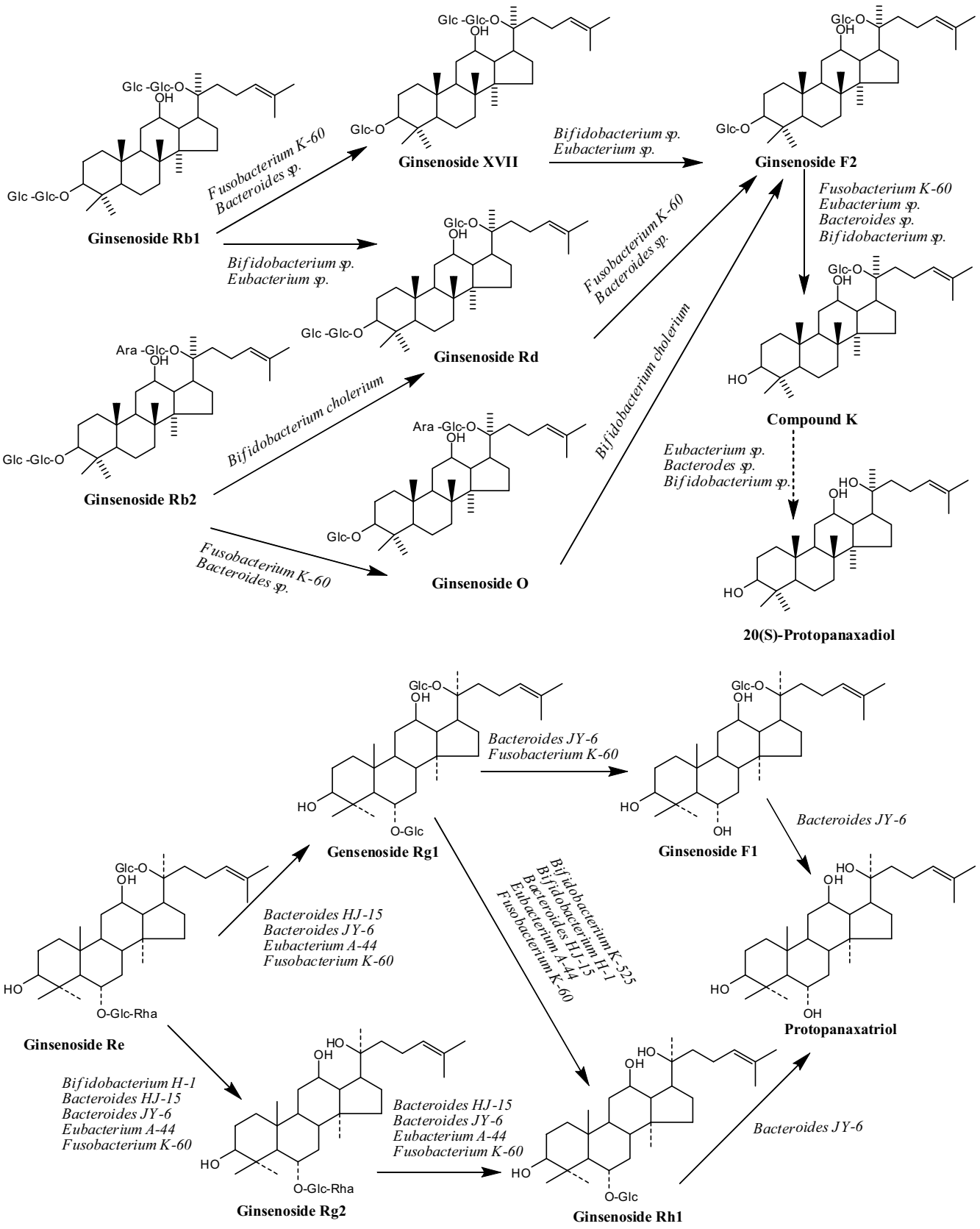

Fig. 2 Proposed metabolic pathways of the Rb1, Rb2, and Re ginsenosides due to the actions of intestinal microflora in the human intestine.

growth of HL-60 and U937 cells (Kang *et al*. 2005), and inhibits TNF-α promoted metastasis by suppressing NF-κB signaling in murine colon cancer cells (Choo *et al*. 2008). Compound K also inhibits inflammatory reactions in LPS-stimulated microglial cells and TNF-α–induced astrocytes, which activate the NF-κB and JNK pathways (Choi *et al*. 2007). Compound K also inhibits MMP-9 expression *via* the AP-1 and MAPK signal pathways in 12-*O*-tetradecanoylphorbol-13-acetate-treated astroglioma cells (Jung *et al*. 2006). Furthermore, it inhibits NO and PGE2 biosynthesis in LPS-stimulated RAW264.7 cells (Park *et al*. 2005), and reduces doxorubicin toxicity in mice (Kang *et al*. 2002). In oxazolone-induced chronic dermatitis in mice, it inhibited histamine- and compound 48/80-induced scratching behaviors (Choo *et al*. 2003; Shin *et al*. 2005a, 2005b). In addition, it activates the DNA repair reaction against UV-in-

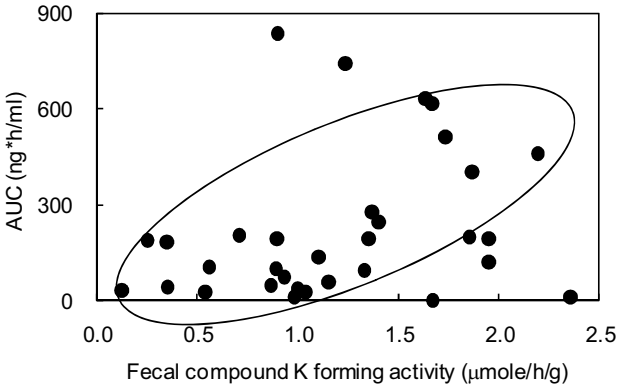

Fig. 3 Scatter diagram between the AUC of compound K and fecal compound K-forming activity for white ginseng powder. Spearman's rank correlation coefficient = 0.402; $P = 0.093$.

duced damage and keratinocyte apoptosis (Kim *et al*. 2004), reduces endotoxin-induced lethal shock and *tert*-butyl hydroperoxide-induced hepatic injury in mice (Lee *et al*. 2005a; Yang *et al*. 2008), inhibits glucose uptake in Caco-2 cells (Chang *et al*. 2007), and improves diabetic markers in *db/db* mice (Han *et al*. 2007). Thus, compound K production from protopanaxadiol ginsenosides may counteract tumor growth, inhibit inflammatory disease, hepatic injury, diabetes, and stress *in vitro* and *in vivo*.

Ginsenoside Rh2 Ginsenoside Rh2 shows hypoglycemic and hypolipidemic effects in mice (Lai *et al*. 2006; Trinh *et al*. 2007), and can promote adipocyte differentiation by activating glucocorticoid receptor. Ginsenoside Rh2 significantly activates AMPK in 3T3-L1 adipocytes and improves insulin sensitivity in rats (Lee *et al*. 2007). It also has a cytotoxic effect on HepG2 and SK-HEP-1 cells (Huang *et al*. 2008), and inhibits the proliferations of prostate cancer cells, colon cancer cells, and human malignant melanoma A375-S2 cells (Fei *et al*. 2002; Kim *et al*. 2004b). Furthermore, it inhibits the metastasis of tumor cells in BALB/*c* mice (Tatsuka *et al*. 2001), and tumor growth in nude mice bearing human ovarian cancer cells (Nakata *et al*. 1998). Ginsenoside Rh2 ameliorates transient focal ischemia in rats (Bae *et al*. 2004; Park *et al*. 2004), and provides potent protection against ischemic brain injury, which suggests that ginseng helps prevent dementia. Furthermore, ginsenoside Rh2 inhibits allergic reactions, such as, degranulation, passive cutaneous anaphylaxis, and contact dermatitis *in vivo* and *in vitro* (Park *et al*. 2003; Bae *et al*. 2006), and was found to ameliorate *tert*-butyl hydroperoxide-induced liver injury (Lee *et al.* 2005b) and cyclophosphamide-induced genotoxic effects in mice (Wang *et al*. 2006). Ginsenoside Rh2 is produced from ginsenoside Rg3 by intestinal microflora *in vivo* and may prevent tumor growth, allergies, ischemia, and hepatic injury *in vitro* and *in vivo*.

Ginsenoside Rh1 Ginsenoside Rh1, a metabolite of ginsenosides Re and Rg1 produced by intestinal microflora, also exhibits various biological effects. Rh1 inhibits iNOS and COX-2 induced by lipopolysaccharide in RAW264.7 cells and in rat peritoneal macrophages (Park *et al.* 2003). It also inhibits oxazolone-induced chronic dermatitis in mice (Park *et al.* 2004a). Ginsenoside Rh1 more potently inhibits inflammatory reactions than ginsenoside Re and potently inhibits allergic reactions, such as, passive cutaneous anaphylaxis and scratching behaviors, by inhibiting the degranulation of mast cells/basophils and vascular permeability, respectively (Shin *et al*. 2006). Ginsenoside Rh1 also exhibit an anticarcinogenic effect in NIH 3T3 cells and has a cytotoxic effect on some tumor cells (Yun *et al*. 2001). Furthermore, ginsenoside Rh1 has an estrogenic effect in MCF9 cells (Bae *et al*. 2005), stimulates the secretion of lipoprotein lipase by 3T3-L1 adipocytes (Masano *et al*. 1996), and increases memory by inducing hippocampal excitability in rats (Wang *et al*. 2009). Information available to date suggests that ginsenoside Rh1 transformed *in vivo* from ginsenosides Re and Rg1 by intestinal microflora reduce tumor growth, ameliorate allergies, and protects against dementia *in vitro* and *in vivo*.

Protopanaxatriol Protopanaxatriol increases memory *via* hippocampal excitability in rats (Wang *et al*. 2009), and has an estrogenic effect on MCF9 cells (Bae *et al*. 2005; Leung *et al*. 2009). Furthermore, it activates PPARγ in 3T3-L1 adipocytes (Han *et al*. 2006). Protopanaxatriol also inhibits COX-2 and iNOS by inhibiting NF-κB activation in RAW264.7 cells stimulated by LPS (Oh *et al*. 2004), and dose-dependently inhibited the proliferative activity of human umbilical vein endothelial cells in an angiogenesis model (Usami *et al*. 2008). Accordingly, protopanaxatriol, which is transformed from ginsenosides Re and Rg1 *in vivo* by intestinal microflora, may inhibit tumor growth and inflammatory disease *in vitro* and *in vivo*.

BIOTRANSFORMED GINSENG

Recently, many biotransformed and fermented ginseng products have been released onto the market, which begs the question 'why is ginseng fermented?' When ginseng is orally administered to humans, its hydrophilic components are inevitably brought into contact with the intestinal microflora, are transformed into absorbable ginsenosides, and then absorbed. Individuals harbor characteristic indigenous strains of intestinal bacteria that have different abilities to metabolize ginsenosides to bioactive compounds (Lee *et al*. 2002; Yim *et al*. 2004). For example, when the metabolic activity of ginsenoside Rb1 and of ginsenoside Rb2 to active compound K was determined, they showed significant inter-individual variations. Therefore, ginsengs containing bioactive and absorbable metabolites, ginsenosides, are valuable for combating various diseases. To develop ginsengs containing these metabolites, the ginsengs are fermented using a range of enzymes or microbes (Bae *et al*. 2003; Trinh *et al*. 2007; Kitaoka *et al*. 2009). However, before these enzymes and probiotics are made available, their safeties and biotransforming activities should be confirmed. If these new products meet these criteria, fermentation biotechnology may provide a valuable means of developing new ginseng products.

Finally, intestinal microflora play an important role in the pharmacological activities of ginseng. Accordingly, evaluations of the pharmacological activities of ginsengs, should consider the metabolisms of their constituents by intestinal microflora.

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