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Bioactivity Enhancement of Herbal Supplements by Intestinal Microbiota Focusing on the Ginsenosides

Huai-You Wang[1], **Lian-Wen Qi**[1,2,*], **Chong-Zhi Wang**[2], and **Ping Li**[1,*]

[1]State Key Laboratory of Natural Medicines (China Pharmaceutical University), Nanjing 210009, China

[2]Tang Center for Herbal Medicine Research and Department of Anesthesia and Critical Care, The University of Chicago, Chicago, Illinois 60637, USA

Abstract

Intestinal microbiota contributes to diverse mammalian processes including the metabolic function of drugs. It is a potential new territory for drug targeting, especially for dietary herbal products. Because most of herbal drugs are orally administered, the chemical profile and corresponding bioactivities of herbal medicines may be altered by intestinal microbiota. Ginseng is one of the most commonly used herb and it is always an attractive natural product to understand. In this review, after briefly introduce the interactions of herbal products and gut microbiota, we discussed the microbiota-mediated metabolism of ginsenosides in ginseng and red ginseng. In particular, the major metabolite Compound K and its pharmacological advances are commented including anticancer, antidiabetic and antiinflammatory effects. In summary, the intestinal microbiota may play an important role in mediating the metabolism and enhancement of bioactivity of herbal medicines.

Keywords

Intestinal microbiota; Ginseng; Red ginseng; Ginsenosides; Compound K

Introduction

The human intestine is densely populated with microorganisms, and is a site where they exert strong influences on human biology as well as drugs' fate (Kullberg, 2008). The entire system of the human intestinal microbiota can be pictured as a 'microbial organ', which are closely associated with diverse processes including the metabolic function of drugs (Palmer *et al.*, 2007; Fishbein *et al.*, 2008; Jia *et al.*, 2008; Kullberg, 2008). Gut microbiota might be a potential new territory for drug targeting, especially for dietary herbal products (Shin *et al.*, 2006; Li *et al.*, 2009).

Herbal drugs have become the basis of traditional medicines for thousands of years (Xutian *et al.*, 2009), and contribute to be considered valuable materials in medicines (Li *et al.*, 2008; Zhao *et al.*, 2009). Most of herbal drugs are orally administered (Gim *et al.*, 2009; Chen *et al.*, 2010; Lin *et al.*, 2010). Active components of these herbal drugs are inevitably in contact with intestinal microflora. Some are transformed by the intestinal bacteria before being absorbed from the gastrointestinal tract. In some cases, gut bacterial drug metabolism is

*Correspondence to: Dr. Lian-Wen Qi or Dr. Ping Li, State Key Laboratory of Natural Medicines (China Pharmaceutical University), Najing 210009, China. fleude@126.com or liping2004@126.com, Tel:/Fax: +86 25-83271379.

associated with bioactivity enhancement and/or toxicity diminishment of the metabolite compared with its parent compound (Shin *et al.*, 2006; Li *et al.*, 2009).

Ginseng is one of the world's most widely used medicinal plants and it is one of the best selling natural products nowadays (Jang and Shin, 2010; Qi *et al.*, 2011a). The major bioactive constituents in ginseng are believe as ginsenoside, a group of triterpene glycosides (Wang *et al.*, 2009; Zuo *et al.*, 2009; Taira *et al.*, 2010). Due to its medicinal effects, ginseng has always been an attractive natural product to study (Zhang *et al.*, 2009; Qi *et al.*, 2011b). Like many other herbal medicines, ginseng is always taken orally. In this form its bioavailability is low because of incomplete absorption (Qi *et al.*, 2010). To date, the biotransformation of ginsenosides to their metabolites by intestinal bacteria has been reported. Some of the metabolites, such as Compound K, have shown various bioactivities.

In this article, we review the role of gut microbiota in mediating the metabolism and enhanced bioactivity of herbal medicines. We first briefly introduce the interactions of herbal products and intestinal microbiota. Taking ginseng as an example, we then discuss the microbiota-mediated metabolism of ginseng and red ginseng. In particular, the major metabolite Compound K and its pharmacological advances are summarized.

Intestinal Microbiota and its Interaction with Herbal Products

Human biological system could be viewed as 'superorganisms' involving an indispensable internal ecosystem of the intestinal microbiota. With the development of global system biology, intestinal microbiota has become a hot topic in life sciences (Gill *et al.*, 2006). Human gut microbiota is believed to consist of well over 500 species representing 5 kingdoms of life and 10 trillion microbial cells. They can be roughly divided as beneficial and pathogenic groups (Versalovic and Relman, 2006; Holmes *et al.*, 2008). The human microbiome contains over 100 times more genes than as does the human genome. Microbial communities *in vivo* include many different bacterial species that are in dynamic, intimate association with each other and with the human host. Accumulating evidence indicates that the intestinal microbiota is a key determiner in energy metabolism and immune function of the host, and has a crucial role in the development of numerous diseases including obesity, diabetes, and even cancers (Ruseler-van Embden *et al.*, 1994; Mazmanian *et al.*, 2008).

Diet is among the most important modifiable determinants of human health. Herbal products are popular dietary supplements since they are natural and therefore safe. An interactive relationship is present between gut microflora and herbal medicines, involving the two important aspects: gut microflora-targeted modulation by herbs and gut microflora-mediated drug metabolism. A large portion of herbs products is water-soluble compositions such as polysaccharides, saponins and inorganic, as well as water-insoluble inorganic materials or polymers. A lot of herbal medicines have been reported as anti-microbial or immunomodulating agents from long-term clinical observations (Schachter, 2008; Wu, 2009; Kano *et al.*, 2010). We believe a large portion of the extraction from herbal products and dietary supplements act as prebiotics or bifidogenic factors by modulating the balance of human gut microbe. From this point, intestinal microbiota might a potential new territory for drug targeting, especially for dietary herbal products. However, limited knowledge has been discovered about the effects of herbs on intestinal microbiota and the molecular details of host–flora interactions are lacking. This subject is interesting but out of the discussion of this review.

Currently, a big challenge for touching herbs is the unavailability of enough quantity and quality of purified single compounds. Therefore, quantitative structure-activity relationship and quantitative metabolism-activity relationship have been summarized, in particular being compared under the same conditions. Many hurdles remain to be overcome in the future for

access to subjects as complex as intestinal microbiota and herbal constituents. For example, better separation and detection systems are required for monitoring complex-system herbs and microbiota, and more powerful computational and statistical tools are indispensable for dealing with large networked data sets.

On the other hand, intestinal microbiota metabolism and biotransformation can also modulate the health effects of dietary herbs by altering their absorption and bioavailability. A diverse and numerous microbiota secrete a various array of enzymes giving them substantial metabolic potential which can have major implications for drug stability. Dietary herbs generally consist of hundreds of constituents. A number of them have been shown to be substrates for these bacterial enzymes. However, the capacity of the intestine for metabolism of drug candidates, and the importance of the intestinal microbiota in influencing the disposition, fate, and toxicity of drugs in the host are often overlooked. The major concern with bacterial drug degradation is the behavior of the metabolite.

Many researchers and pharmaceutical industries tend to approach herbal medicines in a characteristically Western way: isolate active ingredients and test their pharmacokinetics and metabolism one at a time. Actually, the metabolism of herbal medicines is far more complex than that of single compounds. The concentration varies in a large range, component-component metabolic competition exists and parent compounds are unpredictable. Based on *in vitro* and *in vivo* bioactivity evaluation of selected herbal medicines, the influence of intestinal microbiota has been characterized, and some positive perspective on enhancement of bioactivity of botanical metabolites compare to their parent compounds was observed (Li *et al.*, 2009; Shimada *et al.*, 2010).

Ginseng and its Metabolism by Gut Microbiota

After oral administration, ginseng is metabolized extensively by intestinal bacteria (Hasegawa *et al.*, 1996; Hasegawa, 2004; Lee *et al.*, 2009a; Liu *et al.*, 2009). The conversions of ginsenosides in the gastro-intestinal tract have been largely studied using *in vitro* and *in vivo* (Kong *et al.*, 2009; Ruan *et al.*, 2010). The metabolic pathways of protopanaxadiol (PPD)-type and protopanaxatriol (PPT)-type ginsenosides were summarized in Fig. 1 and Fig. 2, respectively. The most popular metabolic pathway is deglycosylation reactions by intestinal bacteria via stepwise cleavage of the sugar moieties (Tawab *et al.*, 2003; Hasegawa, 2004; Liu *et al.*, 2009). In the PPD group, Rb1, Rc, Rb2, Rb3, and Rd are major metabolized to Compound K (Qiang *et al.*, 2006; Yang *et al.*, 2007), demonstrating a preferable selection at C-3 position by intestinal microbiota. In the PPT group, Rg1 and Re are converted to Rh1 and F1 (Wang *et al.*, 2000; Tawab *et al.*, 2003; Yang *et al.*, 2009b). Interestingly, Compound K, an intestinal bacterial metabolite of PPD-type saponins, still contributes to low bioavailability. This possibly resulted from biliary excretion and hepatic metabolism via esterification with fatty acids (Lee *et al.*, 2006; Paek *et al.*, 2006).

As shown in Fig. 1 and 2, oxygenation by intestinal enzymes was observed to be another major metabolic pathway of ginsenosides, in particular for test of single compound (Lai *et al.*, 2009; Yang *et al.*, 2009a). Oxygenation generally occurred on the top-right aliphatic chain (Oian *et al.*, 2005). The gastric acid-mediated hydration reaction was another potential metabolic pathway of ginsenosides.

Tawab reported that after oral administration of Ginsana G115 capsules (4% ginsenosides) to human volunteers, Compound K, F1 and Rh1 or Rg1 were detected to be major metabolites reaching the systemic circulation (Tawab *et al.*, 2003). Recently, the pharmacokinetics of oral administration of ginseng on 32 male subjects was observed. The compound K was absorbed into the circulation 24 hr after intake. There was a correlation

between the compound K transforming activity of ginsenoside-Rb1 and the compound K transforming activity of ginseng extract by intestinal microflora. The biotransformation activity from ginsenoside-Rb1 to Compound K was significantly different among individuals (Lee *et al.*, 2009b). Our ongoing studies in human volunteers observed that ginsenoside Rb1 and Compound K reached the systemic circulation after oral administration of American ginseng (unpublished data). This might lead to different effects of ginseng on individuals.

The following aspects should be highlighted for metabolism and pharmacokinetic study of ginseng: (1) Because of competitive absorption and metabolism, administration of a single ginsenoside or of a ginseng extract may lead to different results. (2) The metabolic profiles of ginsenosides might be different between *in vitro* and *in vivo* results due to higher exposure of compound concentration *in vitro*. Also, the bacterial ginsenoside-hydrolyzing effects are known to be different between humans and experimental mice, as well as for different kind of bacteria. (3) The population of the intestinal bacteria is variable, depending on the conditions of the host, including diet, health, and even stress.

Metabolism of Red Ginseng and its Ginsenosides

Red ginseng is prepared by a steaming process on white ginseng. Red ginseng has long been used in clinic as a single herb or a component of prescription especially in Asian countries. In recent years, we noted that increasing reports have shown various pharmacological effects of red ginseng and its constituents, such as anti-inflammatory, anti-oxidative and anticancer effects (Hong and Lyu, 2011; Jung *et al.*, 2011; Lee *et al.*, 2011). In some cases, the bioactivity of red ginseng was compared with white ginseng, and it seemed the red one showed better potential than the white one (Wang *et al.*, 2007; Sun *et al.*, 2011). The chemical profile differs considerably between white and red ginseng, and has been comprehensively reviewed (Wang and Yuan, 2008; Yuan *et al.*, 2010; Sun *et al.*, 2011). During steaming or heating, the polar ginseng saponins decreased, and less polar ginseng saponins increased.

We have known that gastro-intestinal tract plays an important role in determining the metabolic fate of ginsenosides and mediating the bioactivity of white ginseng. We are curious about the metabolic fingerprinting of red ginseng. Because of the great difference in chemical compositions, red ginseng should have difference metabolites. Although the metabolic profiles of red ginseng have been seldom investigated, the individual ginsenosides have been investigated (Qian *et al.*, 2005a; Qian *et al.*, 2005b; Lai *et al.*, 2009). Fig. 3 summarized the major metabolic pathways and metabolites of ginsenosides (Rh_1, Rg_3, Rg_5 and Rh_2) in red ginseng. Because of unavailability of purified compounds, some major ginsenosides like Rk_1, Rk_3 and Rh_4 in red ginseng have not been investigated. Similar to the metabolic behavior of those ginsenosides in white ginseng, deglucosylation is the most common pathways for red ginseng ginsenosides in gastrointestinal tract. Oxygenation and hydration reaction were also observed. Several pairs of stereoisomers and positional isomers exist in red ginseng (Yang *et al.*, 2007). Few reports have investigated the metabolic difference between isomers. In some publications, geometric isomers were mistaken from each other.(Cai *et al.*, 2003; Qian *et al.*, 2005c; Xie *et al.*, 2005; Zhao *et al.*, 2010)

Pharmacological Advances of Compound K

Compound K (20-O-D-glucopyranosyl-20(S)-protopanaxadiol), also known as IH-901, does not occur naturally in ginseng. It is a major metabolite of protopanaxadiol-type ginsenoside formed by intestinal bacteria via the stepwise cleavage of sugar moieties at C-3 position. After oral administration of ginseng extract in animals and human volunteers, Compound K is a main saponin that reaches the systemic circulation in the body. Several reports have

shown that various pharmacologic actions of ginseng, including anticancer, antidiabetes, and antiinflammation were mediated at least in the part by this compound.

Anticancer

Compound K has been reported to have potential antitumor effects, stronger than its parent compounds ginsenosides Rb_1 and Rd. Several molecular mechanisms exist and collectively converge on various signaling pathways. These pathways include the regulation of the cell cycle, induction of apoptosis, inhibition of angiogenesis, prohibition of invasion, and reduction of inflammatory response. Compound K induced apoptosis in several tumor cell lines by regulating various signaling pathway such as activation of caspase-8 (Cho *et al.*, 2009) and AMP-activated protein kinase (AMPK) (Yoon *et al.*, 2007), suppression of nuclear factor-kappa B (NF-κB) pathways (Choo *et al.*, 2008) and Janus activated kinase 1 (JAK1)-signal transducer and activator of transcription 3 (STAT3) signaling (Park *et al.*, 2011). Also, Compound K suppressed matrix metalloproteinase-9 (MMP-9) expression through inhibition of activator protein-1 (AP-1) and mitogen-activated protein kinase (MAPK) signaling pathways in human astroglioma cells, showing therapeutic potential for controlling the growth and invasiveness of brain tumors (Jung *et al.*, 2006). A recent study showed that CK inhibited basic fibroblast growth factor (bFGF)-induced angiogenesis via regulation of p38 MAPK and AKT in human umbilical vein endothelial cells (Jeong *et al.*, 2010). Though the protective influence of Compound K against cancer has been shown in preclinical studies, this effect needs to be investigated by more scientific clinical trials.

Antidiabetic Effects

Accumulating *in vivo* evidence suggests that Compound K possesses antidiabetic activity(Han *et al.*, 2007). This compound showed beneficial effects on glucose and lipid metabolisms. Involved mechanisms are activation of peroxisome proliferator-activated receptor γ, increase of GLUT expression, and enhancement of PKA-dependent pathways (Han *et al.*, 2007). Selective phosphatidylinositol-3 kinase inhibitor attenuated the Compound K-mediated effects of glucose uptake, suggesting a key role of phosphatidylinositol-3 kinase pathway (Huang *et al.*, 2010). Yong *et al.* found that IH-901 treatment ameliorated an insulin resistance through suppressions of endogenous glucose production and lipogenesis in the liver, and activated phosphorylation of AMPK in the HIT-T15 cells (Yoon *et al.*, 2007). Besides, Compound K shows protective effect against beta-cell death, as might contribute to the previously reported anti-diabetic actions of ginseng by anti-apoptotic (Kim *et al.*, 2010). However, literature evidence of antidiabetic potential of ginsenoside Rb1 was not found, while Rb1 is a parent compound of Compound K. Collectively, compare its parent compound, Compound K might be a promising therapeutic agent improving altered glucose and lipid metabolisms revealed in type 2 diabetes mellitus patients.

Other Effects

The antiinflammatory activities of Compound K have been investigated by both *in vitro* and *in vivo* models (Choi *et al.*, 2007). Tested cell lines include macrophages RAW 264.7 cells (Cuong *et al.*, 2009), astroglial cells (Park *et al.*, 2009), and mononuclear phagocytes (Yang *et al.*, 2008). Key targets were suppressed by Compound K such as NF-κB activation, pro-inflammatory cytokine, mitogen-activated protein kinase, reactive oxygen species, and mitogen-activated protein kinase (Cuong *et al.*, 2009).

Compound K showed more potent hepatoprotective effects then ginsenoside Rb1 on t-BHP-induced hepatotoxicified liver injury (Lee *et al.*, 2005). Because of its immunomodulatory effects, Compound K played a therapeutic role in the treatment of lethal sepsis through the modulation of Toll-like receptor 4-associated signaling via glucocorticoid receptor binding

(Yang *et al.*, 2008). In addition, Compound K can inhibit expression of interferon-γ, thus improving contact dermatitis or psoriasis (Shin *et al.*, 2005).

Summary and Perspectives

Intestinal microbiota can induce comprehensive metabolism of constituents in herbs and might thus increase their bioactivity. Take ginseng as a case, the bioavailability of most original ginsenosides is low, their plasma concentrations may be insufficient to reach to the effects observed under *in vitro* experimental conditions. More *in vivo* preclinical models are essential for evaluation of the clinical effectiveness of the ginseng. Although great progress have been made during the last decades, quality control and batch-to-batch consistency are still big challenges for the development of herbal products. Cultivation conditions can change ginsenoside fingerprinting, thus altering ginseng metabolic biofingerprinting.

Growing evidences have been discovering important functions of the intestinal microbiota in human disease-health and provides new vision for the drug-microbiota interactions. With the emerging and development of system biology, we believe more interesting results will be observed in the future. Further well-designed and systematic studies about influence of dietary herbs such as ginseng on intestinal microbiota will open new targets for herb medicines.

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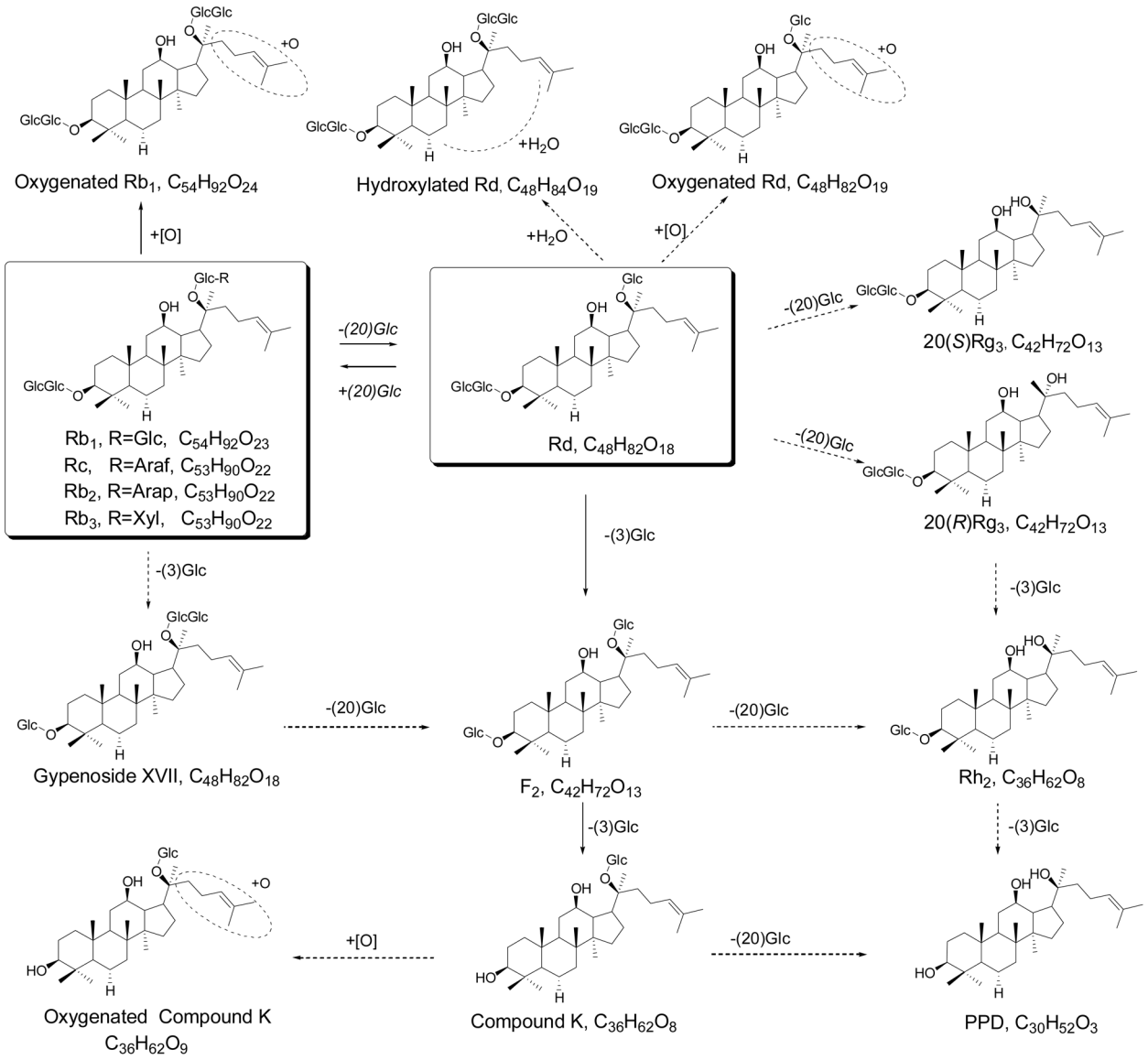

Fig. 1.
Metabolic pathway of protopanaxadiol ginsenosides in ginseng by intestinal microbiota. "→" denotes major pathways; "⇢" denotes additional pathways.

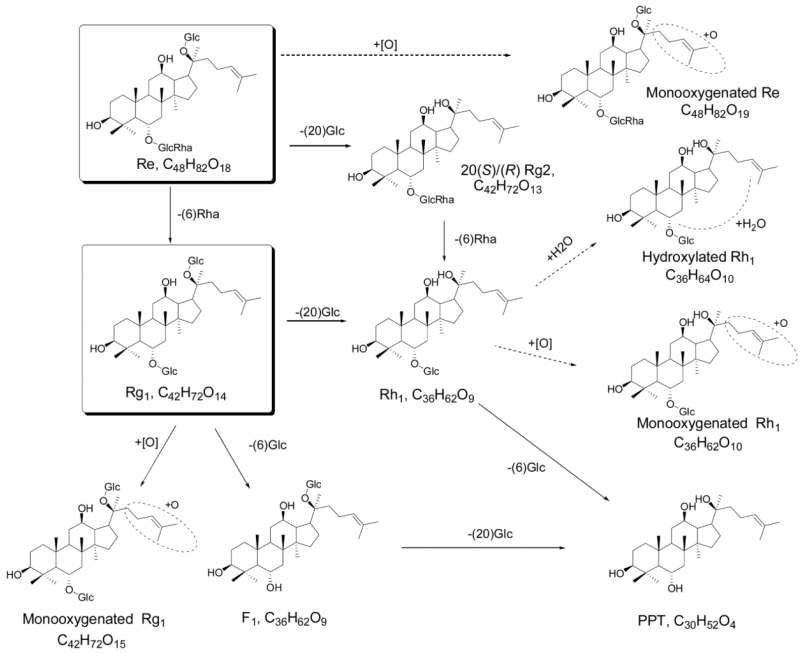

Fig. 2.

Metabolic pathway of protopanaxatriol ginsenosides from ginseng by intestinal microbiota. "→" denotes major pathways; "⇢" denotes additional pathways.

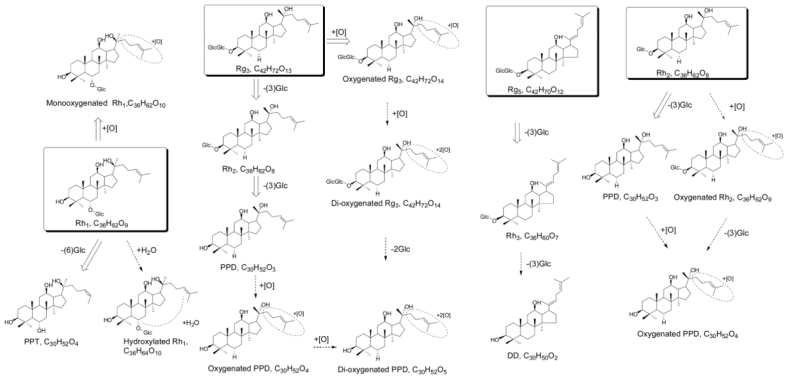

Fig. 3.

Metabolic pathway of ginsenosides in red ginseng by intestinal microbiota. "⇨" denotes major pathways; "⇢" denotes additional pathways.