

Gut microbiota-mediated metabolism of *Panax notoginseng* saponins and its role in pharmacokinetics and pharmacodynamics

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Author contributions

Xuan Zeng and Wei-Wei Su contributed to the conceptualization of this study. Yu-Ying Zheng, Yu-Ling Liu and Wei-Jian Zhang completed the information retrieval and contributed to writing the original draft. Xuan Zeng was responsible for compilation and editing of the manuscript. All authors read and approved the final version of the manuscript.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

PNS, *Panax notoginseng* saponins; PPD, protopanaxadiol; PPT, protopanaxatriol; TCM, traditional Chinese medicine; NA, not available; ADMET, absorption, distribution, metabolism, excretion, and toxicity; TNF, tumour necrosis factor; CASP3, Caspase 3; AKT1, serine/threonine kinase 1; TP53, tumor protein P53.

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Abstract

Panax notoginseng saponins (PNS) are a class of effective ingredients in *Notoginseng Radix et Rhizoma*, a well-known herbal medicine called San-Qi in Chinese. After oral administration, PNS inevitably interacts with gut microbiota, and thus affect the pharmacokinetic profiles and pharmacological effects. To date, studies concerning gut microbiota-mediated metabolism of PNS have not been reviewed systematically. Herein, we outline the metabolic profiles of *Panax notoginseng* saponins mediated by gut microbiota, as well as its role in the pharmacokinetics and pharmacodynamics on the basis of reported data. The metabolic pathways of primary saponins are proposed, and step-by-step deglycosylation is found to be the primary degradation pathways of PNS mediated by gut microbiota. Specific microorganisms and enzymes involved in the metabolic processes were summarized. Gut microbiota is deeply involved in the metabolism of PNS, affects the pharmacokinetic profiles, and produces a series of active metabolites. These metabolites were documented to play an essential role in the efficacy of the parent compounds. Future studies should focus on strengthening the real-world evidence, defining the interaction between gut microbiota and PNS, and developing the strategy for modulating gut microbiota to enhance the bioavailability and efficacy of PNS. These information would be useful for further research and clinical application of PNS.

Keywords: *Panax notoginseng* saponins; gut microbiota; metabolism; pharmacokinetics; pharmacodynamics

Highlights

The metabolism pathways of *Panax notoginseng* saponins (PNS) mediated by gut microbiota were profiled, as well as its role in the pharmacokinetics and pharmacodynamics. Deglycosylation is the primary mode of PNS metabolism mediated by gut microbiota. Metabolites flowed from gut microbiota are crucial for PNS to exert pharmacological activities.

Medical history of objective

PNS are a kind of effective ingredients in *Notoginseng Radix et Rhizoma*, a well-known herbal medicine called San-Qi in Chinese. San-Qi was originally a herbal medicine used by minority ethnic groups in southwest China around 1500 C.E., and was more widely accepted after being recorded in the *Compendium of Materia Medica* (*Ben Cao Gang Mu* in Chinese, 1578 C.E.) compiled by Li Shi-Zhen. Modern pharmacological studies showed that PNS possessed bioactivities in maintaining blood circulation, improving myocardial ischemia, anti-arrhythmia, anti-shock, sedation, improving intelligence, anti-aging, anti-oxidation, anti-cell proliferation and anti-tumor.

Background

Notoginseng Radix et Rhizoma, called San-Qi in Chinese, is the dried root and rhizome of *Panax notoginseng* (Burk) F. H. Chen. It was originally a herbal medicine used by minority ethnic groups in southwest China around 1500 C.E., and was more widely accepted after being recorded in the *Compendium of Materia Medica* (*Ben Cao Gang Mu* in Chinese, 1578 C.E.) compiled by Li Shi-Zhen [1]. To date, more than 200 chemical components have been detected in *Panax notoginseng*, including amino acids, saponins, polysaccharides, flavonoids, volatiles, and acetylenic alcohols [2]. Among these compounds, saponins have been documented as the main effective ingredients. So far, over 70 saponins have been isolated from different parts of *Panax notoginseng* (root, stem, leaf, flower, seed, etc.), but the main components are ginsenoside Rg₁, Rb₁, Rb₂, Rc, Rd, Re, and notoginsenoside R₁ [3, 4]. Most of these monomeric saponins can be classified into two types, including protopanaxadiol (PPD) type and protopanaxatriol (PPT) type. Ginsenoside Rb₁ is the primary PPD-type saponin in San-Qi, while ginsenoside Re, Rg₁ and notoginsenoside R₁ are the main PPT-type saponins. The proportions of these four components in the total PNS are 30%, 2.5%, 20% and 2.5%, respectively [3]. Ginsenoside Rg₁, Rb₁ and notoginsenoside R₁ have shown pharmacological effects in maintaining blood circulation, improving myocardial ischemia, anti-arrhythmia, anti-shock, sedation, improving intelligence, anti-aging, anti-oxidation, anti-cell proliferation and anti-tumor [5–8].

Panax notoginseng is widely used in a variety of oral traditional Chinese medicine (TCM) formulas, therefore contained saponins inevitably interacts with gut microbiota [9]. Gut microbiota is the most important and diverse microbial community in human body. The micro-ecosystem composed of gut microbes and intestinal environment is involved in regulating a series of physiological processes, such as digestion, absorption, development, and immune defense of the host [10, 11]. In recent years, studies have shown that the pharmacologic activities of drugs are not only related to the host itself, but also affected by the microbial community inhabiting the human body. TCM formulas are diverse and complex in composition, and their efficacy is usually related to the specific active metabolites generated in the body, rather than the original compounds. After oral administration, some TCM components are metabolized by intestinal microorganisms in the gastrointestinal tract, and their metabolites are absorbed into the blood to exert pharmacological effects [12]. In some cases, the bioavailability of some TCM components with low fat solubility increase under the metabolic action of gut microbiota [13]. In other cases, intestinal microorganisms can also play a role of

reducing or increasing toxicity by changing the functional groups of some molecules [14]. In addition, changes in gut microbiota caused by environment can also affect the metabolism of some TCM ingredients, indicating the import role of gut microbiota in the pharmacokinetic profiles and pharmacological effects [15, 16].

To date, some in vitro and in vivo studies have been conducted to clarify the interaction between PNS and gut microbiota. However, these results have not been summarized systematically. Herein, we outline the metabolic profiles of PNS mediated by gut microbiota, as well as its role in the pharmacokinetics and pharmacodynamics, so as to provide reference for further research and clinical application of PNS.

Materials and methods

Available references available concerning gut microbiota-mediated metabolism of PNS were collected from online scientific databases including China National Knowledge Infrastructure (<https://www.cnki.net/>), WanFang Data (<https://www.wanfangdata.com.cn/>), PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Science Direct (<https://www.sciencedirect.com/>), SpringerLink (<https://link.springer.com/>), Scopus (<https://www.scopus.com/>), and SciFinder (<https://scifinder.cas.org/>) up to April 2024. The key words included PNS, *Panax notoginseng*, San-Qi, Zao-Gan, gut microbiota, microbe, metabolism, degradation, pharmacokinetics, pharmacodynamics and other related words. All eligible studies are analyzed and summarized in this review.

Gut microbiota and drug metabolism

Gut microbiota is a large and complex microecosystem. Due to its key role in metabolism, gut microbiota has been widely concerned as an “invisible organ” in recent years. Studies have shown that the adult intestinal cavity area is about 300–400 square meters, colonized by about 10¹³–10¹⁴ microorganisms, including bacteria, archaea, fungi, protists, and viruses. Among them, bacteria are the main residents, and more than 99% are anaerobic bacteria [17]. Affected by host genetic background, dietary habits and environmental factors, gut microbiota is diverse and specific [18]. From the phylum level, gut microbiota is mainly composed of Firmicutes (60%–65%), *Bacteroides* (20%–25%), Proteobacteria (5%–10%), and Actinobacteria (approximately 3%) [19]. From the species level, there are dominant and secondary bacterial groups, among which the dominant bacterial groups in the intestinal tracts of healthy adults are mainly *Bifidobacterium*, *Lactobacillus*, and obligatory anaerobic bacteria such as *Spirillum*, *Peptostreptococcus*, *Bacteroides*, etc. [20]. These gut microbes play a very important role in the host physiological functions, including digestion of food, production of important metabolites, promotion of immune system development and maturation, maintenance of gastrointestinal homeostasis, influence of brain function and behavior, and protection of host from pathogen infection [21–24].

Gut microbiota could secrete a wide variety of enzymes and has great potential to transform glycosides, which are an important class of active components in TCM [25]. The free sugar moieties generated by hydrolysis can be used as carbon sources required for microbial growth and reproduction, thus producing more enzymes [26]. Therefore, different microorganisms can play an important role in the biotransformation process of natural products as biocatalysts [27, 28]. A number of studies have pointed out the important contribution of glycosidase, nitroreductase, azoreductase, urease, sulfatase and methylase secreted by intestinal microorganisms in the transformation of glycosides [29]. Among them, α -rhamnosidase, β -glucosidase, β -glucuronidase, β -xylosidase, nitroreductase and other glycosidases are the most critical enzymes for the metabolism of saponins, and deglycosylation catalyzed by these glycosidases is the main pathway to hydrolyze glycosides [30, 31]. Metabolites yielded by deglycosylation are generally more easily absorbed by the intestine and thus have better bioavailability [32]. In addition, gut microbiota

can also drive other metabolic reactions of saponins such as hydroxylation, dehydrogenation, dehydration and demethylation.

Gut microbiota-mediated metabolism of PNS

PNS have high polarity, low fat solubility and low oral bioavailability. Mediated by gut microbiota, most saponins can be metabolized to more absorbable active metabolites [33]. The metabolites of total PNS degraded by human gut microbiota were identified with in vitro incubation method [34]. A total of 45 metabolites were detected, among which ginsenoside F₁, PPT, ginsenoside Rh₂, ginsenoside C-K and PPD had the highest content, and corresponding pharmacological activities were all higher. Deglycosylation is the primary metabolism pathways of PNS mediated by gut microbiota, which also involves hydration, dehydration, hydroxylation, oxidation and so on.

Ginsenoside Rg₁, ginsenoside Rb₁ and notoginsenoside R₁, which are three saponins with highest content in *Panax notoginseng*, were incubated with gut microbiota isolated from female and male Sprague-Dawley rats [35]. The results showed that the degradation of ginsenoside Rb₁ by rat intestinal flora was a slow and progressive process, and the metabolic capacity of male rats was stronger than that of female rats, which may be related to the different proportions of various bacteria in feces of different genders. However, ginsenoside Rg₁ and notoginsenoside R₁ contents remained relatively stable during incubation, suggesting that gut microbiota had different capacity to degrade saponins with different structures. In another study, saponins in *Panax notoginseng* aqueous extract were degraded by human gut microbiota to produce metabolites PPD and PPT under in vitro incubation, while degradation product of rat gut microbiota were only PPT [36]. These results indicated the species differences of gut microbiota-mediated metabolism of PNS, but did not determine whether there are differences in metabolic pathways.

Influenced by diet and disease, the abundance of specific bacteria in the gut microbiota fluctuates dynamically, leading to changes in metabolic capacity of saponins. The metabolic rate of ginsenoside Rg₃

and ginsenoside Rh₂ in the gut microbiota of patients with liver cancer was significantly lower than that of healthy subjects, suggesting that changes in the intestinal microbes of patients with liver cancer had a significant impact on the metabolic rate of above-mentioned two ginsenosides [37]. In addition, different incubation conditions also had certain effects on the metabolic capacity of saponins mediated by gut microbiota. For example, Qian et al. compared the metabolism difference of ginsenoside Rb₁ in the anaerobic and aerobic conditions by step-by-step deglycoside under the action of rat gut microbiota [38]. The metabolic pathway of ginsenoside Rb₁ was proposed as Rb₁→Rd→F₂→C-K. There was no difference in the metabolite types of aerobic and anaerobic incubation, but the metabolic rate of aerobic incubation was faster than that of anaerobic condition. The Rd→F₂ process was considered to be the rate-limiting step of deglycosylation of Rb₁ mediated by gut microbiota.

Reported studies have shown that some fungi and bacteria could hydrolyze the sugar moieties at C-3 or C-20 position of ginsenosides, and metabolize them into aglycones, such as *Aspergillus niger*, *Fusarium* sp., *Penicillium* sp., *Cordyceps sinensis*, *Armillaria mellea*, *Bifidobacterium breve*, *Bacillus* sp., *Lactococcus lactis*, *Lactobacillus plantarum* subsp., *Terrabacter* sp., *Cellulosimicrobium cellulans* sp., *Thermotoga thermarum*, etc. [27]. *Aspergillus niger* can metabolize ginsenosides Rb₁ and Rb₃ into ginsenosides Rd, F₂ and C-K in sequence [39, 40]. *Fusarium* sp. transformed total ginsenosides into ginsenosides C-K by fermentation culture [41]. *Penicillium* sp. degrades ginsenosides through the pathway of Rb₁→Rd→F₂→C-K [42, 43]. Ginsenoside F₂ is converted into ginsenoside C-K by *Bifidobacterium breve* [44]. *Bacillus* sp. hydrolyzes the sugar moieties at C-3 and C-20 positions of ginsenoside Rb₁, to produce ginsenosides Rd, Rg₃, Gyp-XVII and F₂ [44, 45]. The glucosidase gene cloned from *Lactococcus lactis* and *Thermotoga thermarum* was expressed in *Escherichia coli*, yielding glucosidase that can gradually hydrolyze the glucose moieties at C-20 and C-3 positions of ginsenoside Rb₁ [46–48]. Reported specific microorganisms and enzymes involved in the metabolism of PNS were summarized in Table 1 [15, 16, 34, 39–60].

Table 1 Summary of specific microorganisms and enzymes involved in the metabolism of PNS

No.	Parent component	Microbial metabolite	Relate microorganism	Relate enzymes*	References
Total saponins					
1	Total ginsenosides	Ginsenoside C-K	<i>Fusarium</i> sp.	NA	[41, 49]
2	Total PNS	Ginsenoside F ₁ , Ginsenoside Rh ₂ , Ginsenoside C-K, PPT, PPD	<i>Bifidobacterium adolescentis</i> , <i>Lactobacillus rhamnosus</i>	NA	[50]
PPD type saponins					
3	Ginsenoside Rb ₁	Ginsenoside C-K	<i>Ruminococcus</i> sp., <i>Bacteroides</i> sp., <i>Bifidobacterium</i> sp., <i>Bifidobacterium longum</i> H-1	β-Glucosidase	[51, 52]
4	Ginsenoside Rb ₁	Gypenoside XVII	<i>Bacillus</i> sp., <i>Fusobacterium</i> K-60	NA	[44, 45, 53]
5	Ginsenoside Rb ₁	Ginsenoside Rd	<i>Bifidobacterium animalis</i> GM1, <i>Aspergillus niger</i> , <i>Penicillium</i> sp., <i>Bacillus</i> sp., <i>Lactobacillus</i> sp., <i>Eubacterium</i> sp., <i>Bifidobacterium longum</i>	β-Glucosidase	[15, 39, 40, 42–45, 54, 55]
6	Ginsenoside Rb ₁	Ginsenoside F ₂	<i>Bacillus</i> sp.	NA	[44, 45]
7	Ginsenoside Rb ₁	Ginsenoside Rg ₃	<i>Bacillus</i> sp., <i>Lactococcus lactis</i> , <i>Thermotoga thermarum</i>	β-Glucosidase	[44–48]
8	Ginsenoside Ra ₁	Ginsenoside Rb ₂	<i>Bifidobacterium breve</i> K-110	β-Xylosidase	[56]
9	Ginsenoside Rb ₂	Ginsenoside Rd	<i>Bifidobacterium</i> sp., <i>Lactobacillus</i> sp.	NA	[54]
10	Ginsenoside Rc	Ginsenoside Rd	<i>Bifidobacterium</i> sp., <i>Lactobacillus</i> sp.	NA	[54]
11	Ginsenoside Rb ₃	Ginsenoside Rd	<i>Aspergillus niger</i>	NA	[39, 40]
12	Ginsenoside Rd	Ginsenoside F ₂	<i>Aspergillus niger</i> , <i>Penicillium</i> sp., <i>Bifidobacterium</i> sp., <i>Lactobacillus</i> sp., <i>Fusobacterium</i> sp., <i>Bifidobacterium</i> K-103, <i>Bacteroides</i> JY-6	NA	[39, 40, 42, 43, 53, 54]
13	Ginsenoside Rd	Ginsenoside Rg ₃	<i>Lactococcus lactis</i> , <i>Thermotoga thermarum</i> , <i>Bacteroides</i> sp., <i>Microbacterium</i> sp.	β-Glucosidase	[46–48, 54]

Table 1 Summary of specific microorganisms and enzymes involved in the metabolism of PNS (continued)

No.	Parent component	Microbial metabolite	Relate microorganism	Relate enzymes [*]	References
14	Ginsenoside Rg ₃	Ginsenoside Rh ₂	<i>Eubacterium</i> sp., <i>Fusobacterium</i> sp., <i>Bacteroides</i> sp.	β-Glucosidase	[16, 54]
15	Ginsenoside F ₂	Ginsenoside C-K	<i>Aspergillus niger</i> , <i>Penicillium</i> sp., <i>Bifidobacterium breve</i> , <i>Bifidobacterium</i> sp., <i>Bifidobacterium</i> K-103, <i>Lactobacillus</i> sp., <i>Eubacterium</i> sp., <i>Fusobacterium</i> sp., <i>Bacteroides</i> sp., <i>Bacteroides</i> JY-6	NA	[39, 40, 42–44, 53, 54]
16	Ginsenoside C-K	PPD	<i>Roseburia</i> sp., <i>Bifidobacterium</i> sp.	β-Glucosidase	[54, 57]
17	Ginsenoside Rh ₂	PPD	<i>Eubacterium</i> sp., <i>Bacteroides</i> sp.	NA	[54]
PPT type saponins					
18	Notoginsenoside R ₁	Dehydrogenated, oxidative, and demethylated metabolites	<i>Bacteroidetes</i>	Redox enzymes	[58]
19	Ginsenoside Re	Ginsenoside Rg ₁	<i>Bifidobacterium</i> K-103, <i>Bacteroides</i> JY6, <i>Bacteroides</i> HJ15, <i>Eubacterium</i> sp., <i>Fusobacterium</i> sp., <i>Bacteroides</i> sp.	NA	[54, 59]
20	Ginsenoside Re	Ginsenoside Rh ₁ , Ginsenoside F ₁ , PPT	<i>Bacteroides</i> JY-6	NA	[59]
21	Ginsenoside Rg ₁	PPT	<i>Fusobacterium</i> K-60	NA	[52, 60]
22	Ginsenoside Rg ₁	Ginsenoside F ₁	<i>Bifidobacterium</i> K-103, <i>Bacteroides</i> JY6, <i>Bacteroides</i> HJ15, <i>Fusobacterium</i> sp., <i>Bacteroides</i> sp.	NA	[54, 59]
23	Ginsenoside Rg ₁	Ginsenoside Rh ₁	<i>Bifidobacterium</i> K-103, <i>Bacteroides</i> JY6, <i>Bacteroides</i> HJ15, <i>Bifidobacterium</i> sp., <i>Eubacterium</i> sp., <i>Fusobacterium</i> sp., <i>Bacteroides</i> sp.	NA	[54, 59]
24	Ginsenoside Rf	Ginsenoside Rh ₁	<i>Bifidobacterium</i> sp., <i>Bacteroides</i> sp.	NA	[54]
25	Ginsenoside Rh ₁	PPT	<i>Bifidobacterium</i> sp., <i>Bacteroides</i> sp.	NA	[54]
26	Ginsenoside F ₁	PPT	<i>Bacteroides</i> sp.	NA	[54]
27	PPT	Dehydropropanaxtriol	<i>Oscillospira</i> sp., <i>Phascolarctobacterium</i> sp.	NA	[34]

^{*}NA, not available; PNS, *Panax notoginseng* saponins; PPD, protopanaxadiol; PPT, protopanaxatriol.

In general, step-by-step deglycosylation is the primary metabolic pathway of PNS, metabolizing into secondary saponins and aglycones to exert pharmacological effects [61, 62]. Based on reported studies, the metabolic pathways of PPD-type and PPT-type saponins mediated by gut microbiota were plotted in Figure 1, 2, respectively [49, 63, 64].

Role of gut microbiota on the pharmacokinetics of PNS

Pharmacokinetic studies aim to understand the behavior of drugs in vivo, including absorption, distribution, metabolism, and excretion. PNS will inevitably interact with gut microbiota after oral ingestion, which will affect the absorption and metabolism profiles of saponins. Herein, we evaluated the effects of gut microbiota mediated metabolism on the pharmacokinetic properties of PNS using chemometrics approach. Based on database resources, the molecular properties of ginsenoside Rb₁, PPD, notoginsenoside R₁, and PPT were listed in Table 2 [65, 66]. Through the deglycosylation mediated by gut microbiota, the LogP value, solubility, surface area and polarity parameters of PNS were greatly transformed, which led to the change of pharmacokinetic properties.

Pseudo germ-free rodents are an effective strategy for evaluating the role of gut microbiota in metabolic processes in vivo, typically through antibiotic intervention to deplete their resident microbiota. Specifically, normal control and pseudo germ-free rats were used to investigate the in vivo metabolic profiles of PNS mediated by gut microbiota [13]. A total of 73 metabolites were identified in the feces of normal control rats, while only 11 PNS metabolites were detected in pseudo germ-free rats, highlighting the profound role of gut

microbiota on the metabolism of PNS. In another study, a rat model of gut microbiota disturbance was established by lincomycin intervention, so as to investigate its effects on the pharmacokinetics of ginsenoside Rg₃ [16]. Compared with the normal control group, the C_{max} and area under the curve of ginsenoside Rh₂, the active deglycosylated metabolite of ginsenoside Rg₃, were significantly reduced in the dysbiosis rats. This may be due to the decrease of β-glucosidase activity in gut microbiota of rats treated with lincomycin, which affected the deglycosylation of ginsenoside Rg₃ and then changed the pharmacokinetic behavior of ginsenoside Rg₃ and ginsenoside Rh₂.

These results suggest that the metabolism of PNS was found to be greatly affected by gut microbiota. For example, Proteobacteria may affect the deglycosylation of PNS by regulating the activity of glycosidase, and *Bacteroides* may promote the oxidation-reduction metabolism of PNS by improving the activity of corresponding enzymes [58]. In addition, individual differences in PNS metabolism have been observed to be related to the composition and abundance of gut microbiota [15]. The abundance of *Bacteroidetes* S24-7, *Alcaligenaceae*, and *Erysipelotrichaceae* were higher in the gut microbiota of individuals with fast metabolism. *Bifidobacterium animalis* GM1 was further isolated, which could convert ginsenoside Rb₁ to ginsenoside Rd. These specific intestinal bacteria was deemed as the dominated microorganism in the metabolism of PNS. And the abundance changes of these gut microbiota can modulate the metabolism of ginsenosides in intestine, and subsequently affect the pharmacokinetic profiles.

Role of gut microbiota on the pharmacodynamics of PNS

The pharmacological activity of the compound is closely related to its structure. Mediated by gut microbiota, PNS underwent deglycosylation, dehydrogenation, oxidation, dehydration, hydroxylation and other reactions, producing a series of metabolites with different activities from the parent compounds [67]. A number of studies have proved that PNS metabolites generated through the deglycosylation mediated by gut microbiota have stronger pharmacological activity [68].

Ginsenoside R_{h2} and PPD were defined as the main metabolites of ginsenoside Rg₃, and found to inhibit the proliferation of tumor cells with in vitro experiments [69]. Niu et al. determined the anti-tumor activity of ginsenosides Rb₁ and its metabolites on A/J mouse metastatic lung cancer LMI cells [70]. The metabolites ginsenosides F₂ and CK were found to have significant anti-tumor activity, while

prototype ginsenosides Rb₁ did not have such activity. Another in vitro experiments confirmed that ginsenoside Rb₁ has no obvious anti-tumor effect on human colon cancer HT-29 cells, but its deglycosylated product ginsenoside CK has a strong anti-tumor effect [71]. Herein, Ginsenoside C-K, the metabolite of PPD-type saponins, has stronger anti-tumor activity in vivo and in vitro than that of parent compounds [27]. Similar results were observed for PPT-type saponins. Lee et al. compared the anti-tumor activity of ginsenoside Rg₁, Re, and their metabolites PPT under different administration strategies [72]. All three ginsenosides were found to have strong anti-tumor cell metastasis effects after oral administration, while only PPT has anti-tumor activity when administered intravenously. The results indicated that the anti-tumor effect of ginsenoside Rg₁ and Re after oral administration was contributed by their metabolites PPT.

Table 2 The molecular properties of ginsenoside Rb₁, PPD, notoginsenoside R₁, and PPT

Molecular properties	Ginsenoside Rb ₁	PPD	Notoginsenoside R ₁	PPT
ALogP	-1.198	5.789	-0.11	4.62
Molecular solubility	-6.095	-8.328	-5.424	-7.191
Molecular volume	773.12	372.15	663.36	374.89
Molecular surface area	1077.6	500.93	917.35	513.89
Molecular polar surface area	377.29	60.69	298.14	80.92
ADMET absorption level	3	1	3	0
ADMET blood-brain barrier level	4	1	4	2
ADMET solubility	-8.235	-5.769	-6.783	-4.532

PPD, protopanaxadiol; PPT, protopanaxatriol; ADMET, absorption, distribution, metabolism, excretion, and toxicity.

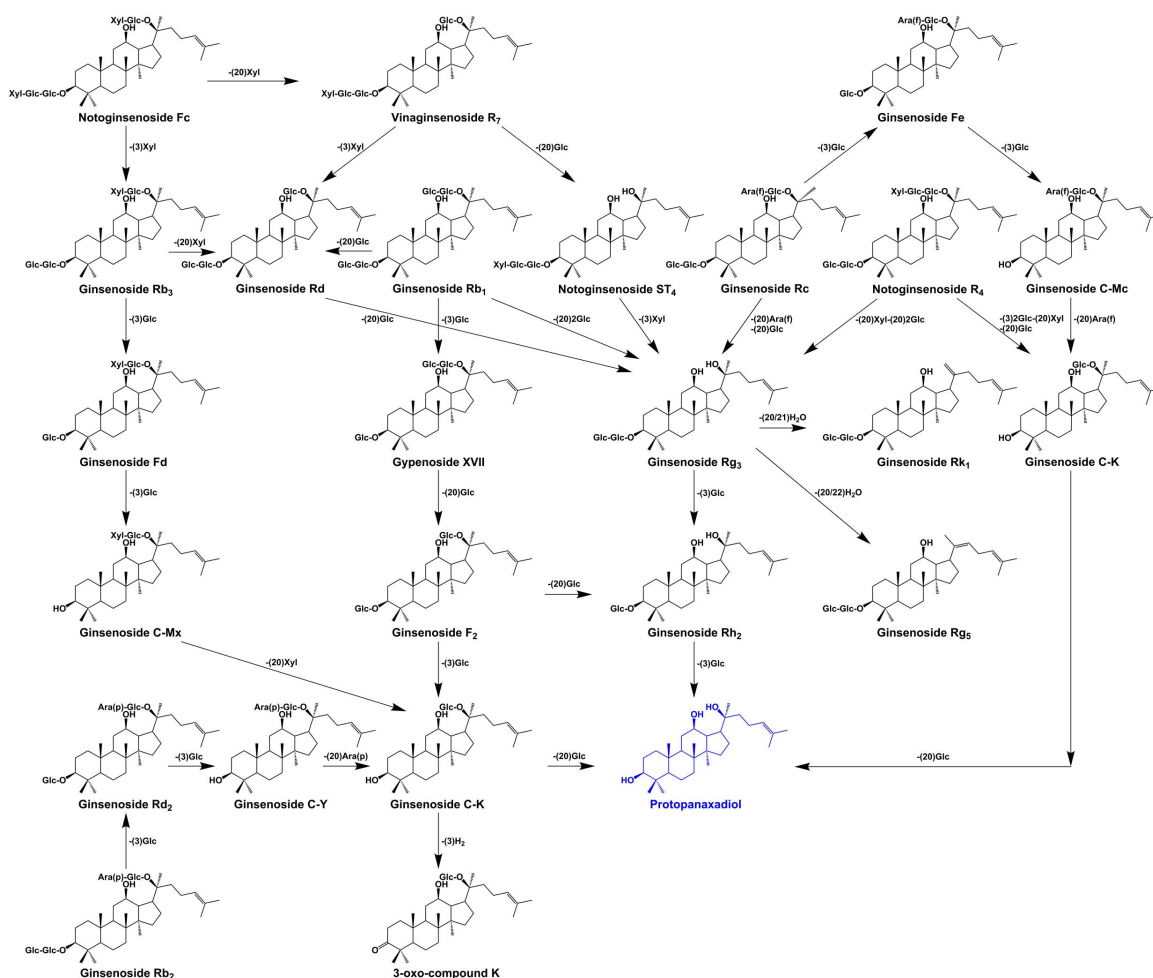


Figure 1 Proposed metabolism pathways of PPD-type saponins mediated by gut microbiota

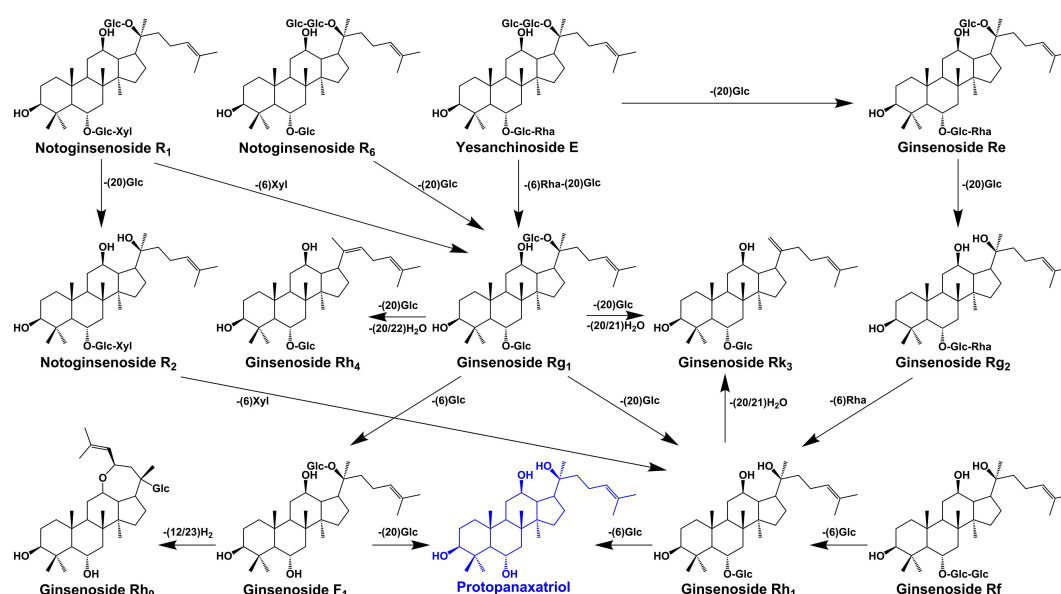


Figure 2 Proposed metabolism pathways of PPT-type saponins mediated by gut microbiota

In vitro incubation experiments showed that PNS had no obvious inhibitory effect on *Akkermansia* and *Bacteroides*, but the main metabolite generated by gut microbiota, ginsenoside C-K could inhibit the growth of *Bacteroides hetaiotaomicron* and *Bacteroides virgatus* [73]. Ginsenoside C-K has therapeutic effects on colitis and is one of the pharmacodynamic substances of PNS metabolized by gut microbiota. In another study, ginsenoside Rh₁, a metabolite of ginsenoside Re degraded by gut microbiota, was found to be more quickly absorbed into the body to exert estrogen-like effects [59]. These studies indicate that PNS metabolites produced by gut microbiota have a variety of pharmacological activities, and play an essential role in the efficacy of the parent compounds.

In addition, taking insenoside Rb₁, PPD, notoginsenoside R₁ and PPT as examples, we evaluated the effects of gut microbiota mediated deglycosylation on the pharmacodynamic properties using network pharmacology and molecular docking strategies [74, 75]. The corresponding targets of mentioned four compounds were obtained from SwissTargetPrediction (<http://www.swisstargetprediction.ch/>), and the potential targets of PNS for disease treatment were acquired from DisGeNET (<https://www.disgenet.org/search>) using the keywords of “Angina pectoris”, “Coronary arteriosclerosis”, “Coronary heart disease”, and “Coronary thrombosis”. There were 410 targets corresponding to the four compounds and 1,819 disease-related targets, among which 159 targets were common (Supplementary Figure S1). The protein-protein interaction network was constructed using the String (<https://string-db.org/>) in combination with Cytoscape, so as to identify the crucial targets. Subsequently, to reveal the interactions between mentioned four compounds and target proteins at the molecular level, molecular docking was performed on five crucial targets, i.e. TNF (tumour necrosis factor), CASP3 (Caspase 3), AKT1 (serine/threonine kinase 1), TP53 (tumor protein P53), and STAT3 (signal transducer and activator of transcription 3) (Supplementary Table S1). The molecular docking was conducted with Autodock Tools (Version 1.4.6). Calculated docking affinity were listed in Supplementary Table S2. The docking scores of ginsenoside Rb₁, protopanaxadiol, notoginsenoside R₁ and protopanaxatriol to TNF, CASP3, AKT1, TP53, and STAT3 proteins were ≤ -5.0 kJ/mol, indicating that mentioned four compounds bind closely to the crucial target proteins. A lower docking score suggests a stronger binding force. The docking affinity of protopanaxadiol to TNF, CASP3, AKT1, and TP53 were lower than that of ginsenoside Rb₁, especially the TNF. Similar results were also observed in protopanaxatriol and notoginsenoside R₁, which again confirmed the effect of deglycosylation mediated by gut microbiota on the bio-activities of PNS. The molecular spatial structure changes after deglycosylation

make the compound bind more closely to some target proteins and show better biological activity. The 3D diagrams of molecular docking for ginsenoside Rb₁, notoginsenoside R₁, protopanaxadiol, and protopanaxatriol to TNF were shown in Supplementary Figure S2. The docking affinity of PPD to TNF, CASP3, AKT1, and TP53 were lower than that of ginsenoside Rb₁, suggesting a stronger binding force. Similar results were also observed in PPT and notoginsenoside R₁, which again confirmed the effect of deglycosylation mediated by gut microbiota on the bio-activities of PNS. The molecular spatial structure changes associated with deglycosylation make the compound bind more closely to some target proteins and show better biological activity. Therefore, future studies pharmacodynamic studies of PNS should fully take into account the role of gut microbiota.

Summary and future prospects

Herein, the metabolic profiles of PNS mediated by gut microbiota were summarized systematically, as well as its role in the pharmacokinetics and pharmacodynamics. Mediated by gut microbiota, PNS were extensively engaged in deglycosylation, giving rise to a series of metabolites. Gut microbiota could modulate the metabolism of PNS in the intestine, and then affect their pharmacokinetic and pharmacodynamic profiles. However, there were some issues to be settled in the future.

Firstly, current researches on PNS metabolism mediated by gut microbiota were mainly conducted in vitro models or rodent animals, as well as other studies on pharmacokinetics and pharmacodynamics. The real-world evidence about these biological processes in the human body is limited. For example, the differences in PNS metabolism among different enterotype microbiota are not yet clear, and the effects of gastrointestinal diseases and antibiotic interventions on the pharmacokinetics and pharmacodynamics of PNS are also uncertain.

Secondly, in-depth and systematic studies are necessary to define the interaction between gut microbiota and PNS. Germ-free rodent animals have been used to investigate the role of gut microbiota on the pharmacokinetics and pharmacodynamics of PNS, but the main focus is on the impact of gut microbiota abundance. Information concerning the effects of specific microorganisms or enzymes on the metabolism of certain saponins is still scarce, as well as corresponding regulatory mechanisms. Meanwhile, more researches are called for defining the modulation effects of PNS on gut microbiota, especially on its impacts on pharmacokinetics and efficacy after long-term ingestion. Given that PNS metabolites produced by gut microbiota have a variety of pharmacological activities, follow-up studies should pay more attention to the role of gut microbiota when exploring the

pharmacological mechanism of PNS.

Thirdly, there is a lack of precise strategies for regulating gut microbiota to enhance the bioavailability and efficacy of PNS. At present, probiotics and prebiotics have been used to improve the gut microbiota of patients, but their effects on PNS metabolism and efficacy are still unclear. It is worth exploring how to modulate gut microbiota through convenient and safe intervention strategies, so as to overcome the low bioavailability of PNS and improve treatment effectiveness.

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