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Review Article

Methods on improvements of the poor oral bioavailability of ginsenosides: Pre-processing, structural modification, drug combination, and micro- or nano- delivery system

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ABSTRACT

Panax ginseng Meyer is a traditional Chinese medicine that is widely used as tonic in Asia. The main pharmacologically active components of ginseng are the dammarane-type ginsenosides, which have been shown to have anti-cancer, anti-inflammatory, immunoregulatory, neuroprotective, and metabolic regulatory activities. Moreover, some of ginsenosides (eg, Rh2 and Rg3) have been developed into nutraceuticals. However, the utilization of ginsenosides in clinic is restrictive due to poor permeability in cells and low bioavailability in human body. Obviously, the dammarane skeleton and glycosyls of ginsenosides are responsible for these limitations. Therefore, improving the oral bioavailability of ginsenosides has become a pressing issue. Here, based on the structures of ginsenosides, we summarized the understanding of the factors affecting the oral bioavailability of ginsenosides, introduced the methods to enhance the oral bioavailability and proposed the future perspectives on improving the oral bioavailability of ginsenosides.

1. Introduction

The root of Panax ginseng Meyer, commonly known as ginseng, is a traditional Chinese medicine that has gained popularity in modern times as a raw material for adaptogens [1]. Ginseng possesses a range of beneficial properties including antioxidant, anti-inflammatory, antimicrobial and anticancer activities [2]. As a result, ginseng-based products are launched in commercial markets as tonic (e.g. Celestial Seasonings Ginseng, Centrum Herbals Ginseng, Nature Made's Chinese Red Panax Ginseng and Korean Ginseng Extract from Nature's Way) [3]. In the food industry, ginseng is also used as an ingredient, especially in chewing gums, candies and beverages [4].

The main active compounds in ginseng are ginsenosides, which exhibit various pharmacological activities. Ginsenosides can be classified as dammarane-type, oleanane-type, and ocotillol-type [5], with dammarane-type ginsenosides (hereafter abbreviated as ginsenoside(s)) being the primary pharmacologically active components [2]. Conventionally, ginsenosides were studied as anti-cancer, anti-inflammatory and immunoregulatory agents [6]. While recent researches have uncovered their potential to treat other diseases such as rheumatoid arthritis (e.g. compound K) [7], metabolic syndrome (e.g. ginsenoside Rg3, Rg1, Rb and Rh1) [8], neurological diseases (e.g. ginsenoside Rd) [9], and cardiovascular diseases (e.g. ginsenoside Rg1, Rb1 and F1) [10].

Interestingly, there is a contradiction between the bioactivity and the physicochemical property of ginsenosides. Ginsenosides are involved in various biological processes in cytomembranes [11] and interact with the proteins in cytosol [12]. Moreover, they can interact with transcription factors and then regulate their transcriptional activities [13]. This indicates that ginsenosides should possess excellent lipophilicity to penetrate the layers of biofilms. However, the dammarane skeleton of ginsenosides leads to poor hydrophilicity, while the glycosyls decrease their lipophilicity, which results in limited solubility in majority of solvents. Consequently, the intestinal permeability and the oral bioavailability of ginsenosides are relatively low. To be specific, the oral

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bioavailability of ginsenoside Rb 1, Rb2, Rb3, Rd, Rg3, Rh2, compound K (CK), Re and Rg1 are all below 15%, only ginsenoside PPD possesses the oral bioavailability higher than 40% [14].

Therefore, it is of significance to improve the oral bioavailability of ginsenosides. However, the mechanisms of intestinal absorptions of ginsenosides are inexplicit, consequently, the methods to enhance the oral bioavailability of ginsenosides are not well-directed yet. Hence, this review (1) summarizes the factors affecting the oral bioavailability of ginsenosides (including structure of ginsenosides, efflux and gut microbiota), (2) and introduces methods for improving the oral bioavailability of ginsenosides based on related mechanisms, and (3) proposes other potential ways to enhance the intestinal absorptions of ginsenosides.

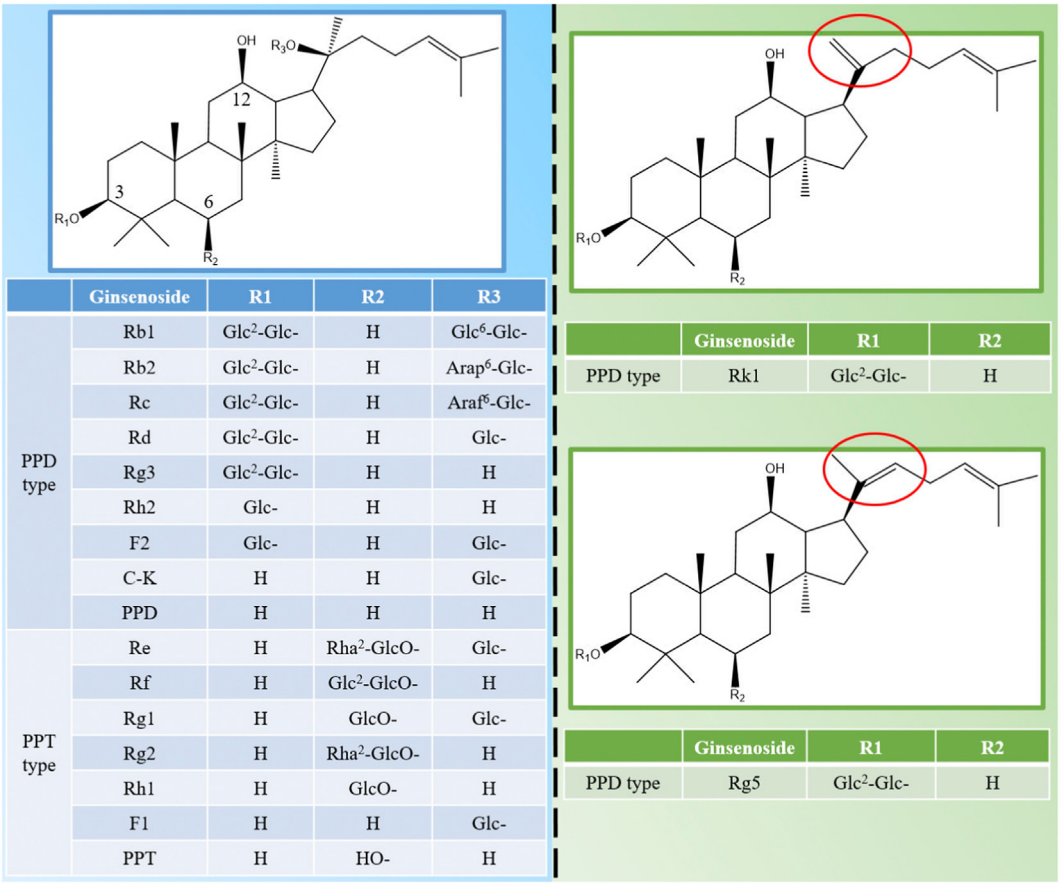
2. The factors affecting the oral bioavailability of ginsenosides

2.1. Structure of ginsenosides

The dammarane-type ginsenosides could be divided into two categories based on their structure: protopanaxadiol (PPD) type and protopanaxatriol (PPT) type. They are characterized by the presence or absence of substituent at the C-6 position: PPD-type ginsenosides lack this substituent, while PPT-type ginsenosides have either hydroxyls or glycosidic bonds. (Fig. 1). Both types of ginsenosides exhibit anticancer, anti-inflammatory, and immunomodulatory activity, which suggests that the difference of their structures is unlikely to be the determining factor of their bioactivities. However, the difference in their structures can affect the oral bioavailability of these two types of ginsenosides. Previous studies have demonstrated that the concentration of PPD was higher than that of PPT in the plasma of rats after oral administration. PPD possessed lower excretory rate in the plasma [15], which resulted in that the absolute bioavailability of PPD was higher than that of PPT. Interestingly, ginsenoside Rb1, a PPD-type ginsenoside, has been proved to possess lower absolute bioavailability than ginsenoside Rg1 (a PPT-type ginsenoside) [16,17], which indicated that the oral bioavailability of ginsenoside might be affected by some other factors.

As shown in Fig. 1, Rb1 contains four glycosyls while Rg2 only contains two glycosyls, and the hydroxyls carried by glycosyls would decrease the lipophilicity of ginsenoside. Consequently, it is more challenging for Rb1 than Rg2 to pass through the cells in the intestinal tract. It has been also confirmed that the uptake of PPD (containing no glycosyl) by Caco2 cells was higher than ginsenoside Rh2 (containing 1 glycosyl) [18,19]. For the permeability in Caco2 cell model, Niu et al [20] compared the absorptions of different ginsenosides and ranked them in the following descending order: ginsenoside CK (containing one glycosyl), Rd (containing three glycosyls), Rb1 (containing four glycosyls). In summary, the ginsenoside with fewer glycosyls is more lipophilic and has a higher oral bioavailability. On the other hand, more glycosyls lead to a higher molecular weight, which makes the ginsenoside less absorbable than the one with low molecular weight.

Considering both PPD-/PPT- type and numbers of glycosyls, Kim et al [21] concluded the permeability rankings as follows: Rg1 (PPT type, 2 glycosyls) ≥Rf (PPT type, 2 glycosyls), Re (PPT type, 3 glycosyls) ≥ Rc (PPD type, 4 glycosyls) > Rb1 (PPD type, 4



	Ginsenoside	R1	R2	R3
PPD type	Rb1	Glc^{2}-Glc-	H	Glc^{6}-Glc-
	Rb2	Glc^{2}-Glc-	H	Arap^{6}-Glc-
	Rc	Glc^{2}-Glc-	H	Araf^{6}-Glc-
	Rd	Glc^{2}-Glc-	H	Glc-
	Rg3	Glc^{2}-Glc-	H	H
	Rh2	Glc-	H	H
	F2	Glc-	H	Glc-
	C-K	H	H	Glc-
	PPD	H	H	H
PPT type	Re	H	Rha^{2}-GlcO-	Glc-
	Rf	H	Glc^{2}-GlcO-	H
	Rg1	H	GlcO-	Glc-
	Rg2	H	Rha^{2}-GlcO-	H
	Rh1	H	GlcO-	H
	F1	H	H	Glc-
	PPT	H	HO-	H

	Ginsenoside	R1	R2
PPD type	Rk1	Glc^{2}-Glc-	H

	Ginsenoside	R1	R2
PPD type	Rg5	Glc^{2}-Glc-	H

Fig. 1. The structures of dammarane-type ginsenosides.

glycosyls) > Rb2 (PPD type, 4 glycosyls). This suggests that furanose is more beneficial for passing through Caco2 cells when compared with pyranose. Additionally, the glycosidic bond at the C-20 position would improve the permeability when compared with that at C-3 and C-6 position (Fig. 1), which could also be supported by Ha et al [22] who found CK permeated across cytomembrane more easily than Rh2.

Taken together, PPD-type ginsenosides possess higher oral bioavailability than PPT-type, meanwhile the glycosyls (especially those at the C-3 and C-6 position) are generally considered as the disadvantages for the oral absorption.

2.2. Efflux

P-glycoprotein (P-gp) is a member of ATP-binding cassette superfamily which possesses the efflux activity to pump the xenobiotics into extracellular matrix [23]. Activation of P-gp can lead to the decline of the absorptions of ginsenosides (Fig. 2). The verapamil and Cyclosporine A (P-gp inhibitors) could decrease the efflux ratio of ginsenoside Rh2, which indicated that P-gp participated in the efflux of Rh2 [24,25]. However, not all ginsenosides could be the substrates of P-gp. It has been proved that the absorptions of ginsenoside Rb1, Rb2, Rc, Rd, Rg2, and Rg3 might be inhibited by P-gp, while the absorptions of Rh1, F1, Re and Rg1 were not affected by P-gp inhibitors [26]. This reveals that PPD type ginsenosides, rather than PPT type, are more likely to be the substrates of P-gp. As shown in Fig. 3, the binding site of P-gp substrate has two loose binding pockets in the two terminals, and a compact cavity in the center [23]. Therefore, it is difficult for the binding site of P-gp substrate to provide enough space to the glycosyls at the C-6 position in PPT type ginsenosides.

Interestingly, ginsenosides are not only the P-gp substrate but also the P-gp inhibitors. Ginsenosides could interact with P-gp protein at the azidopine site to increase the intracellular accumulation of other P-gp substrate [27]. Rh2 has been proved to enhance the absorption of digoxin [28,29], fexofenadine [28], etoposide [28] and ritonavir [30]. Ginsenoside PDQ, CK, PPD and PPT have been also confirmed to improve the absorption of rhodamine 123 or digoxin [26,31]. Additionally, ginsenoside Rg1, Re, Rc, and Rd were also found to moderately inhibit the drug efflux pump and increase drug accumulation [27]. These results indicate that the dammarane skeleton is the pharmacophore contributing to the P-gp inhibition, but the side chain might have no effects on P-gp inhibiting activity [32]. However, glycosyls might weaken the inhibitory effect on P-gp. Because the hydrophobicity is required for binding as P-gp inhibitors (Log P $\geq$ 2.92), while the glycosyls would increase hydrophilicity [33].

2.3. Body state and gut microbiota

It is acknowledged that the physical state could influence the metabolism within the body. As expected, the oral bioavailability of ginsenosides could be affected by the physiological state (such as diet intervention or disease). After the diet intervention with high-fat foods, the oral bioavailability of ginsenoside CK and PPD increased in human body [34]. This is probably because the high-fat diet might increase the micellar solubilization and wettability of drugs [34]. And in diabetic rats, oral bioavailability of Rb1 was enhanced and the urinary excretion of Rb1 decreased [35]. After the oral administration of ginsenoside Rg3 in walker 256 tumor-bearing rats, the areas under the plasma level/time curve (AUC) of Rg3 and Rh2 both decreased, which indicated that the transformation of Rg3 into Rh2 might also be inhibited [36].

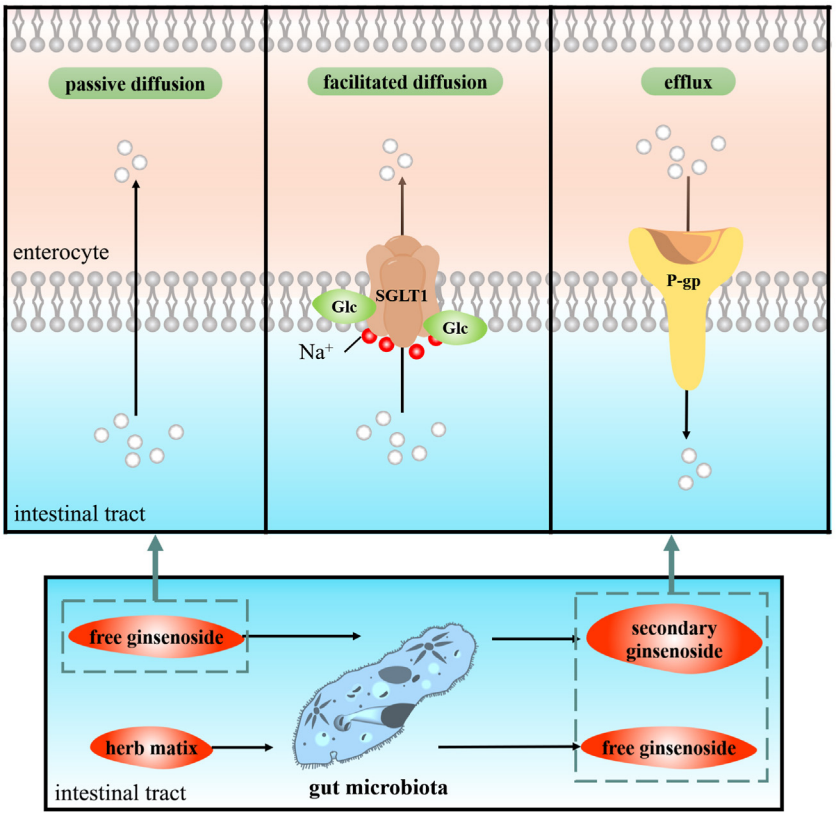


Fig. 2. The possible mechanisms involved in intestinal absorption of ginsenoside.

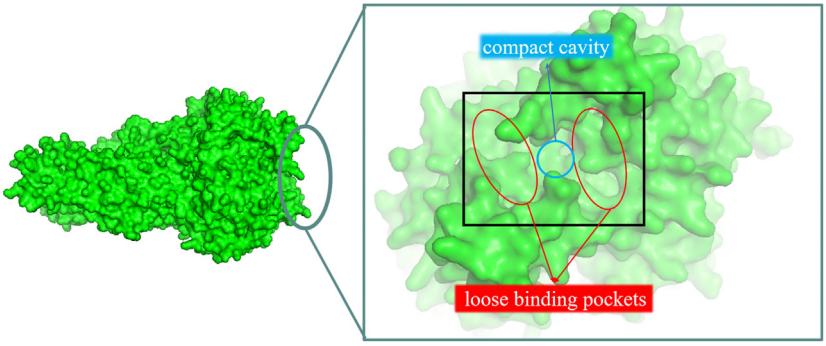


Fig. 3. The 3D-structure of P-glycoprotein substrate binding site.

Table 1
The Pre-processing of ginseng for improving the oral bioavailability of ginsenosides

Product	Pre-processing	Models	Effects		References
			AUCs (*in vivo*)	Transepithelial transport (*in vitro*)	
White ginseng	The fresh ginseng was sun-dried until moisture content was below 12%.	Rats	↑ 3.0-fold (Rg1) ↑ 1.2-fold (Re) ↑ 2.1-fold (Rb1) ↑ 2.7-fold (Rd)		[49,50]
Frozen ginseng	The fresh ginseng was freeze-dried under −80 °C until moisture content was below 12%.	Rats	↑ 3.7-fold (Rg1) ↑ 5.4-fold (Re) ↑ 3.0-fold (Rb1) ↑ 1.9-fold (Rd)		
Red ginseng	The fresh ginseng was washed and steamed at 98°C for 3 h and then was dried at 65°C until moisture content was below 12%.	Rats	↑ 3.6-fold (Rg1) ↑ 1.5-fold (Re) ↑ 2.8-fold (Rb1) ↑ 1.4-fold (Rd)		
		Human			[49]
Black ginseng	The fresh ginseng was washed and treated with nine cycles of steaming at 98°C for 3 h and drying at 65°C.	Human	↑ 1.8-fold (total gisenoside, compared with red ginseng)		
Sulphur-fumigated ginseng	After the 48 h-fumigation with sulfur powder, the ginsengs were aeration-dried at 40 °C for 12 h.	Caco2 cell		↑ 1.5-fold (Rg1) ↑ 1.2-fold (Re)	[52]
Fermented ginseng	The *Phellinus linteus* were inoculated into the sterilized red ginseng extract. The fermentation was carried out at 25°C, with an aeration rate of 1.0 vvm for 5 days under shaking rate of 150 rpm.	Everted intestinal sac		↑ 1.2-fold (total ginsenosides)	[46]
	Lactobacillus sakei HY7802 was used to ferment the red ginseng extract which was pre-incubated with0.8% CytolasePCL5, 0.8% Sumizyme AC, and 0.8% Rapidase C80Max at50°C for 72 h.	Human and rats	↑ 115-fold (CK, human) ↑ 6.3-fold (CK, rat)		[47]

AUC: the area under the plasma concentration time curve.

Interestingly, even though immunosuppression can always be found in tumor environment, ginsenosides F2, Rg3, Rd, Rh1, Rg1 and CK were found to be more abundant in immunosuppressed rats [37]. Moreover, the mental disease can also affect the oral bioavailability of ginsenosides. In rats with depression, the absorptions of ginsenoside Rh1, Rb1, Rc and Rd were enhanced in comparison to normal rats [38]. In a rat model of Alzheimer's disease, the absorption of Rd was improved but absorptions of Rb1 and Re remained at similar levels to the normal rats [39].

These phenomena might be attributed to the gut microbiota: a large number literature have demonstrated that the state of health had effects on the gut microbiota, which in turn affected the absorptions of ginsenosides [35,37,40–43]. The metabolic status can vary depending on the different state of health, and the different metabolic status would result in diverse gut microbiota composition [40]. Eventually, the gut microbiota might regulate the oral bioavailability of ginsenosides in three ways: 1) the gut microbiota might release the ginsenosides binding to (or trapped in) the food/drug matrix (e.g. fiber, protein), which could increase the amount of free ginsenosides [44]; 2) the gut microbiota might regulate the metabolic process of ginsenosides (e.g. deglycosylation) [45]; 3) the gut microbiota might regulate the intestinal permeability [35] (Fig. 2). Although the *Bifidobacterium animalis* GM1 has been confirmed to promote the deglycosylation of ginsenosides *in vitro* [40], the specific strains responsible for enhancing the oral bioavailability of ginsenosides have not been elucidated yet. At the very least, future researches should explore the correlation between gut microbiota and ginsenosides absorption.

What is more, the ginsenosides have been proved to be capable of regulating the gut microbiota to enhance the conversion of the original ginsenosides to metabolic secondary ginsenosides [41], which indicates a forward feedback loop between ginsenosides and gut microbiota.

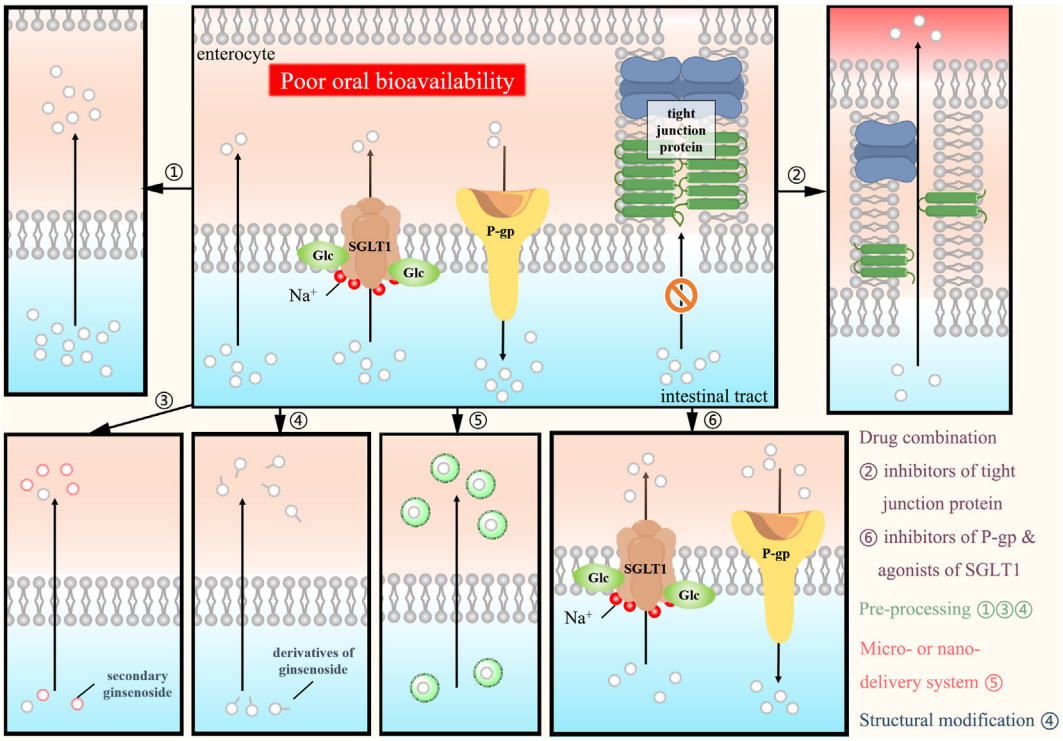


Fig. 4. The methods to improve the oral bioavailability of ginsenosides and the underlying mechanisms.

3. The strategies to improve the oral bioavailability of ginsenosides

3.1. Pre-processing

Since the gut microbiota could enhance the oral bioavailability of ginsenosides by deglycosylation or releasing them from matrix, the absorption might increase before the gut microbiota phase if the raw materials undergo specific pre-processing (Table 1). There is no doubt that the fermentation *in vitro* could serve as an appropriate alternative. Ryu et al [46] fermented the red ginseng with *Phellinus linteus* and observed higher intestinal permeability of ginsenosides (especially secondary metabolites) in fermented ginseng other than non-fermented ginseng. The *Lactobacillus sake*i HY7802 was also utilized to ferment red ginseng, and enhanced the oral bioavailability of CK in rats and human [47]. In the further researches, screening of strains used for fermentation can be further refined, and the genetic engineering could be employed to obtain the strains with high deglycation activity.

Meanwhile, the thermal treatment has also been demonstrated to facilitate the release of phytochemicals in food matrix and improve the deglycosylation [48]. Red ginseng is produced by steaming and drying fresh ginseng at high temperatures (> 65 °C). And if the procedure is repeated nine times, the black ginseng is obtained. Yoo et al [49] found that the absorptions of Rg3, Rg5, Rk1 and Rh2 in black ginseng were 6-24 folds higher than those in red ginseng. Furthermore, the AUC of total ginsenosides in black ginseng was also higher than that in red ginseng. Freeze-drying has also been reported to enhance the bioavailability of phytochemicals. The Rg1, Re, Rb1 and Rd in freeze-dried ginseng were more readily absorbed into the plasma than those in untreated ginsenosides [50]. Sulphur-fumigation is a traditional post-harvest handling of ginseng and can induce chemical transformation of ginsenosides [51]. Shen et al [52]found that the uptakes of Rg1 and Re were increased in the sulphur-fumigated ginseng, while the efflux ratios of Rg1 and Re were decreased.

3.2. Structural modification

The structure of ginsenoside has a significant impact on its oral bioavailability, therefore, the modifications of ginsenoside structure may help improve the oral bioavailability. It has been confirmed that structural modification could enhance the bioactivities of ginsenosides (e.g. anticancer effects, anti-inflammatory effects) [53]. Meanwhile, certain modifications can also improve the absorptions of ginsenosides. The cell membrane is mainly composed of lipids, therefore enhancing the lipophilicity of ginsenosides would be a sound method to improve the membrane permeability (Fig. 5). For instance, octyl ester of CK exhibited higher uptake and lower efflux ratio in Caco2 cell than CK [54]. Similarly, the octyl esterification of Rh2 also decrease the efflux ratio of Rh2 [25]. The long-chain aliphatic group might be responsible for this difference, because the center region of P-gp substrate binding site is confined to interact with the long-chain aliphatic group at C-12 position (Fig. 2).

However, the modifications of structure targeting at enhancing oral bioavailability of ginsenoside are not investigated systematically. Present researches mainly focus on the esterification of ginsenosides. While the elimination reaction to reduce hydroxyls and intramolecular-cyclocondensation both could enhance the lipophilicity of the molecules, which might draw attentions in future. Certainly, enhancing the lipophilicity would not be the only solution: sulfated Rh2 has been proved to possess higher bioavailability than the original type [55] (Fig. 5). The effects of these modifications on the oral bioavailability of ginsenosides could be further investigated and a structure-activity relationship between ginsenosides and oral bioavailability could be summarized.

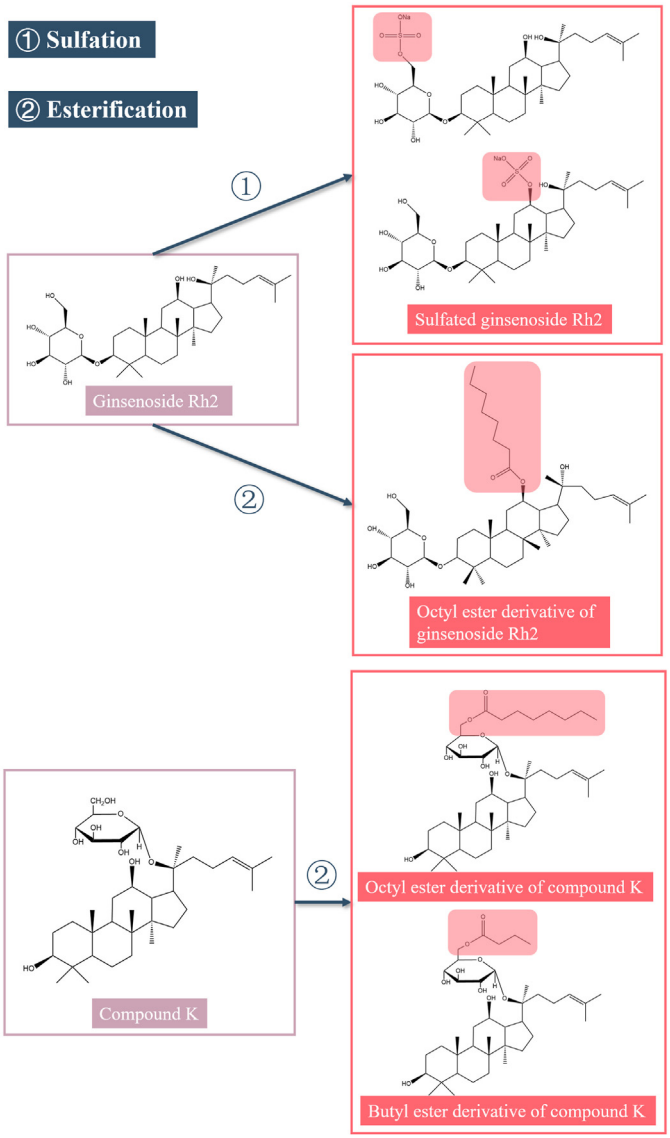


Fig. 5. The structure of ginsenoside derivatives which opposes higher oral bioavailability than original types.

3.3. Drug combination

3.3.1. Prebiotics

Prebiotic fiber can alter the composition of gut microbiota, which indicates that prebiotics might enhance the oral bioavailability of ginsenosides [56–58] (Fig. 4 &Table 2). Initially, prebiotic fibers (e.g.NUTRIOSE) were confirmed to enhance the oral bioavailability of the secondary metabolites of ginsenosides (e.g. ginsenoside CK) [56]. Subsequently, the NUTRIOSE-containing diet has been proved to promote the absorption of Rd in rats [57]. Prebiotic intervention (with fructooligosaccharide, galactooligosaccharide, or fibersol-2) for 14 days also increased the absorption of Rd, as well as the absorptions of Rb1, F2, and CK [58]. Notably, polysaccharides from ginseng are also been found to stimulate absorption of ginsenoside through their effects on gut microbial metabolism, which could be observed in both normal rats and rats exposed to over-fatigue and acute cold stress models [42,43].

3.3.2. Clinical drugs

Since the ginsenosides are the P-gp substrates, the absorptions of ginsenosides could be enhanced by P-gp inhibitors (Table 2). The combination of verapamil and ginsenosides has been proved to improve the oral bioavailability of ginsenosides as mentioned above. Borneol is a traditional Chinese medicine and has also been prove to be a P-gp inhibitor [59]. Numerous studies have revealed that borneol could facilitate the intestinal absorption of ginsenosides Rg1, Re, Rb1, and Rd [60,61]. Moreover, this facilitating effect appears to be independent on the ginsenoside state, namely, the borneol can promote the absorptions of ginsenosides in free-form, in ginseng extract and even in traditional Chinese medicine compound recipe. Piperine has also been studied as a P-gp inhibitor for ages [62]. And enhancement on oral bioavailability of Rh2 was observed when Rh2 was co-administrated with piperine [63].

Actually, not only the P-gp inhibitors can improve the oral bioavailability of ginsenosides, but other drugs (e.g. aspirin and adrenaline) can exert absorption-facilitating function by different mechanisms (Table 2). In rat model, aspirin could also improve the absorptions and permeabilities of Rb1, Rg1 and Rd [64]. It has been reported that aspirin could inhibit the expression of tight junction proteins, consequently, increase the intestinal permeability [64]. Xiong et al [65] found that co-administration with adrenaline could be an efficient way to promote the absorption of Rg1. The phloridzin and Na^+ depletion were found to reverse the enhancement by adrenaline [66]. Adrenaline can increase the expression of SGLT1 (a transporter protein dependent on Na^+ and glucose) in intestinal epithelial cells. However, phloridzin can inhibit the activity of glycoside conjugates, and Na^+ could provide potential difference for the uptake of SGLT1 substrates [66]. Taken together, SGLT1 might participate in the active transport of ginsenoside Rg1 (Fig. 2). Despite these findings, further evidences should be provided to prove that SGLT1 is responsible for the intestinal absorptions of a majority of ginsenosides.

3.3.3. Medicinal herbs

A large number of medicinal herbs (including ginseng itself) have been demonstrated to possess inhibitory effects on P-gp or tight junction proteins [27]. And the polysaccharides in medicinal herbs exhibit the ability to regulate the gut microbiota [67]. Therefore, medicinal herbs might be a potential option to combine with ginseng for higher oral bioavailability of ginsenosides (Table 2).

Acorus gramineus is a traditional Chinese medicine utilized to treat age-related diseases, and has been proved to inhibit the intercellular tight junction [68]. Consequently, co-administration of *Acorus gramineus* and ginseng could potentially improve the oral bioavailability of ginsenosides [69]. The lignans in *Schisandra Chinensis* have been proved to be P-gp inhibitors [70]. Hence, *Schisandra* lignans extract was found to increase the AUCs of Rb2, Rc and Rd in rats, and decrease the efflux ratios of ginsenoside Rb2, Rc, Rg2, Rg3, Rd and Rb1 in Caco-2 model [70]. The traditional Chinese medicine compound recipe is a combination of various medicinal herbs at a specific ratio. The ginsenosides in Ding-Zhi-Xiao-Wan (consist of *Ginseng Radix*, *Poriacocos*, *Polygala Radix*, and *Acorus Tatarinowii Rhizoma*) have been proved to possess higher permeability and lower efflux ratio in Caco2 model than those in single herb [71]. The pre-processing can also affect oral bioavailability of ginsenosides in traditional Chinese medicine compound recipe. To obtain the traditional decoction of Qixue–Shuangbu (consist of *Ginseng Radix et Rhizoma*, *Astragali Radix*, *Angelicae Sinensis Radix*, *Paeoniae Radix Alba*, *Lycii Fructus*, *Polygoni Multiflori Radix*, *Polygonati Odorati Rhizoma*, *Polygonati Rhizoma*and *Citri Reticulatae*

Table 2
Drug combinations improving the oral bioavailability of ginsenosides

Additional stimulus	Ginsenosides	Model	Administration	Effects		References
				AUCs (*in vivo*)	Transepithelial transport (*in vitro*)	
NUTRIOSE	CK	Rats	The dietary interventions were carried out with2.5%, 5% or 10% NUTRIOSE-containing diets for 14 days.	↑ 2.8-fold		[56]
	Rd	Rats	After 2-week dietary intervention with NUTRIOSE, the ginsenoside Rb1, ginseng extract, or vehicle were administrated to rats orally.	↑ 1.3-fold		[57]
Fructo-oligosaccharide Galacto-oligosaccharide Fibersol-2	Rb1	Rats	The rats were administrated with FOS, GOS, and fibersol-2 (1g/d), respectively, for two weeks. And then intragastric administration of Rb1 (100 mg/kg) was performed on the last day.	↑ 2.2 ~ 3.1-fold (Rb1) ↑ 1.8 ~ 2.4-fold (CK, metabolites) ↑ 1.2 ~ 1.9-fold (F2, metabolites) ↑ 1.7 ~ 2.1-fold (Rd, metabolites)		[58]
ginseng polysaccharides	Rb1	Rats	Rat sreceived oral administration of ginseng polysaccharides (228 mg/kg/day) for 1 week. And then rat was intragastrically administrated with Rb (110 mg/kg).	↑ 2.2-fold (Rb1) ↑ 3.2-fold (CK, metabolites) ↑ 1.3-fold (PPD, metabolites) ↑ 1.4-fold (Rd, metabolites)		[42]
	Rb1	Caco-2 cell	Rb1 (10 μM) was loaded to the apical or basolateral side in transwell plates in absence or presence of ginseng polysaccharides(250 μg/ml) loaded to the opposite side.		↑ 1.6-fold	[42]
	mixture	Rats (over-fatigue and acute cold stress model)	Rats received oral administration of oligofructose (200 mg/kg) or ginseng polysaccharides extracts (200 mg/kg) for 14 days. On the 14th day, the rats were intragastrically administered with ginsenosides solution (500 mg/kg).	↑ 1.5-fold (Rg2) ↑ 2.2-fold (Rd) ↑ 2.3-fold (Rg3)		[43]
Borneol	mixture	Rabbits	The rats were given Panax notoginseng (3.0mL/kg) orally alone or in the combination with borneol (1.42 g to 50 mL ginseng extract)	↑ 2.6-fold (Rg1) ↑ 2.6-fold (Re)		[60]
	mixture	Human	Orally administration with drugs equivalent to 90 pills of compound Danshen dropping pills with or without borneol.	↑ 1.8-fold (Rg1) ↑ 3.3-fold (Rb1)		[61]
Piperine	Rh2	Rats	The rats were administered with Rh2 (10 mg/kg) orally alone or in the combination of piperine (10 or 20 mg/kg).	↑ 2-fold		[63]
Aspirin	mixture	Rats	The rats were administered with the *Panax notoginseng* Saponins (31.25 mg/kg) orally alone or in combination with aspirin (20.83 mg/kg)	↑ 1.5-fold (Rg1) ↑ 1.6-fold (Rb1) ↑ 2.6-fold (Rd)		[64]
Adrenaline	Rg1	Caco-2 cell	Rg1 (1 mg/ml) was added to each well in absence or presence of adrenaline (0.01-10 mM).		↑ 6.2-fold	[65]
		Rats	Rg1 (200 mg/kg) with or without adrenaline (4mg/kg) was administered orally.	↑ 28-fold		[65]
Acorus gramineus	mixture	Rats	*Panax quinquefolius* (0.54 g/kg) was administered orally alone or with AG (0.54 g/kg).	↑ 1.4-fold (Rb1) ↑ 2.0-fold (Rb2) ↑ 1.3-fold (Rd) ↑ 1.5-fold (Re)		[69]
Schisandra lignans	mixture	Caco-2 cell	Caco-2 cells were incubated with *Schisandra* lignans extract (2.0 and10.0 mg/mL) for 1 h before the addition of ginseng extract (100 mg/mL).		↑ 2.1-fold (Rb2) ↑ 2.9-fold (Rc) ↑ 2.6-fold (Rg2) ↑ 2.7-fold (Rg3) ↑ 3.0-fold (Rd) ↑ 2.5-fold (Rb)	[70]

Table 2 (*continued*)

Additional stimulus	Ginsenosides	Model	Administration	Effects		References
				AUCs (*in vivo*)	Transepithelial transport (*in vitro*)	
		Rats	Acute effect: the rats received Schisandra lignans extract(500 mg/kg) 2 h before the orally administration of ginseng extract (120 mg/kg) Long-term effects: the rats were administrated with Schisandra lignans extract (500 mg/kg) orally for 10 days, then ginseng extract (120 mg/kg) was administered intragastrically.	↑ 1.9-fold (Rb2) ↑ 2.0-fold (Rc) ↑ 1.7-fold (Rg2) ↑ 2.4-fold (Rg3) ↑ 2.5-fold (Rd) ↑ 2.1-fold (Rb)		[70]

AUC: the area under the plasma concentration time curve.

Table 3
Micro- or nano- delivery systems for improving the oral bioavailability of ginsenosides

Delivery system	Additives	Ginsenoside or raw materials	Model	Effects		References
				AUCs (*in vivo*)	Uptake or transepithelial transport (*in vitro*)	
Micro- or nano-particles	Soluplus	CK	Rats (35 mg/kg)	↑ 2.0-fold		[79]
	Silicon Dioxide,	Korean red ginseng extract	Rats (375 mg /kg)	↑ 1.6-fold (Rb1) ↑ 1.6-fold (Rb2) ↑ 1.8-fold (Rc) ↑ 1.7-fold (Rd)		[80]
	PEG-PLGA polymers	25-OCH3-PPD	Caco-2 cell (1 or 5 μg/mL)		↑ 6.0-fold	[81]
			Rats (100 mg/kg)	↑ 26-fold		[81]
	BSA, N-hydroxy succinimide ester of FA	Rg5	MCF-7 cells		↑ 1.8-fold (uptake)	[82]
	γ-cyclodextrin	CK	Rats (30 mg/kg)	↑ 1.7-fold		[83]
		Re	Rats (100 mg/kg)	↑ 1.6-fold		[84]
	Glyceryl-tristearate, soybean oil, Tween 80 and Span 80	F1	Caco-2 Cell (300 μg/ml)		↑ 1.5-fold	[85]
Micro- or nano-emulsion	Phospholipid and PEG400	25-OCH_3-PPD	Rats (20 mg/kg)	↑ 3.6-fold		[86]
	Cremophor® EL,glycerin andLabrafil® M1944	25-OCH_3-PPD	Rats (5 mg/kg)	↑ 9.8-fold		[76]
	Miglyol, Tween-20, and labrasol	Rh1, Rh2	Rats (18.75 mg/kg)	↑ 2.6-fold (Rh1) ↑ 2.8-fold (Rh2)		[87]
Liposome	Phospholipids, plurololeique CC 497, Labrafac cc and Capmul MCM	*Panax notoginseng*saponins extracts	Rats (600 mg/kg)	↑ 10.8-fold (Rg1) ↑ 6.5-fold (Rb1)		[89]
	egg yolk phosphatidylcholine, cholesterol	Rg3	Rats (0.25, 0.5 or 1 mg/kg)	↑ 1.5-fold		[91]

PEG: polyethylene glycol, AUC: the area under the plasma concentration time curve.

Pericarpium), the Qixue—Shuangbu was prepared and decocted with boiling water [72]. The compound tincture was obtained if the Qixue—Shuangbu was decocted with wine-processing [73]. Significantly, the ginsenosides in the compound tincture were absorbed into plasma more easily than those in the traditional decoction [72].

In fact, other components in ginseng could also act as accelerants for the absorption of ginsenosides. Bae et al found that Rh2 and Rg3 were more readily absorbed into the plasma of rats when administrated in ginseng extract [74]. And the AUC of Re can also be increased when co-administrated with ginseng berry extract [75].

3.4. Micro- or nano- delivery system

Microencapsulation or nano-emulsion is an efficient way to stabilize the compounds and improve the bioavailability (Table 3). On the one hand, the tiny particles would be readily be absorbed into body. The tiny droplet size of a micro (or nano)-system have large interfacial surface areas, which facilitates the release and absorption of the compounds [76]. For example, the bioavailability of Rb, Rc, Rd and Re in ultrafine granular powder ginseng are higher than those in common powder [77]. And the micronized Rh2 is

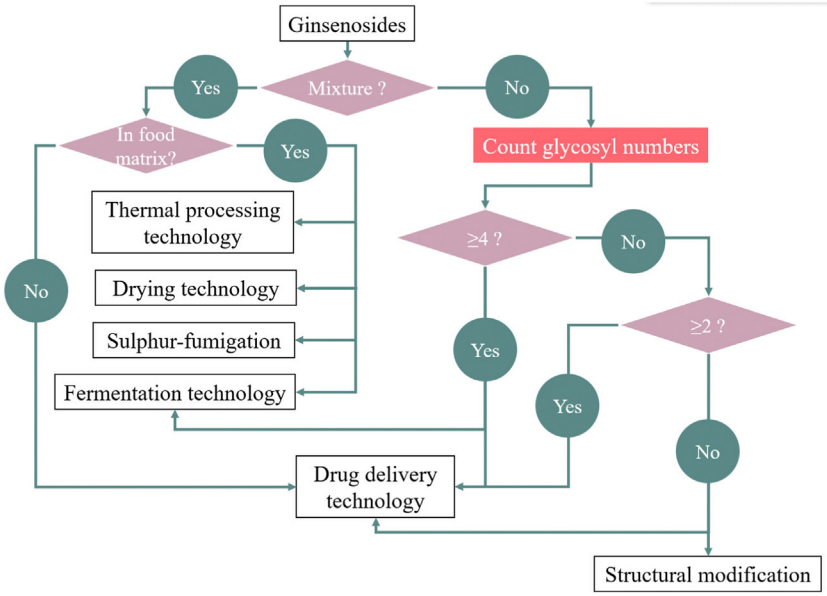


Fig. 6. The program flowchart for choosing the methods to improve the bioavailability of ginsenosides. Notes: the proposed technology is not the only option but the highly recommended one.

more likely to be absorbed into plasma than native Rh2 [78]. On the other hand, micro- or nano- delivery system could also modify the lipophilicity or hydrophilcity of compounds, thereby, enhance the penetrability of compounds (Fig. 4).

3.4.1. Micro- and nano-particles

The self-nanomicellizing solid dispersion system is a technique for embedding a variety of active ingredients within a solid polymer matrix (Table 3). The ginsenoside CK was successfully encapsulated in Soluplus, and the oral bioavailability of CK was found to be increased [79]. Silicon dioxide can also embed ginsenosides, and increase intestinal permeability of Rb1, Rb2, Rc and Rd [80]. The polyethylene glycol (PEG) is another widely used encapsulating material, Voruganti et al [81] prepared ginsenoside 25-OCH_3-PPD loaded PEG-poly(lactic-co-glycolic acid) nanoparticles, which resulted in increased abundance of 25-OCH3-PPD in plasma and tissue of rats. The three macronutrients (proteins, carbohydrates and lipids) can be degraded or utilized easily in human body, therefore they are acknowledged wall material for particles. Dong et al [82] encapsulated Rg5 in bovine serum albumin modified with folic acid, which enhanced the uptake of Rg5. Igami et al [83] and Li et al [84] used gamma-cyclodextrin to coat CK and Re, respectively. They both found the AUCs of ginsenosides in rats were elevated after the encapsulation implemented. And the ginsenoside F1 has been proved to permeate across Caco2 more easily when encapsulated by soybean oil and glyceryl tristearate [85].

3.4.2. Micro- and nano-emulsion

Emulsification is a common strategy to improve the bioavailability of non-amphiphilic compounds (Table 3). The ginsenoside 25-OCH_3-PPD could be dispersed in the emulsion prepared by phospholipid and PEG, resulting in significantly higher AUC of 25-OCH_3-PPD when compared to its free form [86]. The self-microemulsifying drug delivery system containing 25-OCH_3-PPD can also be obtained by using Cremophor® EL as the surfactant, glycerin as the cosurfactant, and Labrafil® M1944 as the oil. As expected, this resulted in an increase in bioavailability of 25-OCH3-PPD [76]. With ginsenoside Rh1, Rh2, Miglyol (as oil phase), Tween-20 (as emulsifier) and labrasol (as co-emulsifier) being mixed, the emulsion containing ginsenosides has been formed. This led to enhanced permeabilities of Rh1 and Rh2, as well as increased concentrations of Rh1 and Rh2 in the plasma and tissues of rats [87].

3.4.3. Liposome

Liposomes mainly consist of phospholipids and cholesterol, and have similar structure with the biofilm [88], which is advantageous for the transport of drugs across the intestinal tract (Table 3). The thin-film hydration method is a classical way to prepare liposomes, and the Rg1, Rg2, Rg3 and Rb1 were all successfully encapsulated in liposome via this method [88–90]. The polycarbonate membrane extrusion method is another alternative for liposome preparation: Yu et al [91] obtained the ginsenoside Rg3-containing liposome made up of egg yolk phosphatidylcholine via this method. As a result, the cellular uptake or bioavailability of Rg1, Rg2, Rg3 and Rb1 were significantly enhanced with the delivery of liposome.

Additionally, prebiotics that promote probiotic reproduction have been shown to be benefits for the oral bioavailability of ginsenosides. Meanwhile, various prebiotics are widely used as coating materials in micro- (or nano-) system. Therefore, the utilization of prebiotics (e.g. inulin and pectin) during preparing micro- or nano-delivery system has the potential to enhance oral bioavailability of ginsenosides in the future.

Taken together, drug delivery systems might be generally applicable for improving the oral bioavailability of various ginsenosides (Fig. 6). On the contrary, the structural modification has its limitation when dealing with ginsenosides with several glycosyls (Fig. 6). Because their high molecular weights become the primary obstacles for oral absorption, which structural modification could not address adequately. Deglycosylation via fermentation technology may provide a solution for improving the oral bioavailability and enhancing the pharmaceutical effects of ginsenosides with multiple glycosylation sites (Fig. 6).

4. Conclusion

The ginsenosides are the main pharmacologically active components in ginseng that are in high demand across Asia. However, the poor oral bioavailability of ginsenosides presents significant challenges to their practical application. Both efflux caused by P-gp and low lipophilicity resulting from the glycosyls contribute to the poor oral bioavailability. Fortunately, the P-gp inhibitors and the compounds regulating the gut microbiota have been proved to improve the oral bioavailability of ginsenosides. Meanwhile, the methods to modify the lipophilicity of ginsenosides (e.g. Structural modification and delivery system) have also shown promise for improving intestinal absorption. Given these findings, the micro- or nano-delivery system containing P-gp inhibitors or prebiotics might be a popular strategy for enhancing the oral bioavailability of ginsenosides in the future.

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