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Synergistic Regulation of Glucolipid Metabolism by Ginseng Polysaccharides and Ginsenosides: Divergent Microbiota Modulation and Convergent Activation of Intestinal Gluconeogenesis

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Abstract:

Ginseng polysaccharides (GPS) and ginsenosides are two major bioactive components of Panax ginseng, both exhibiting regulatory effects on glucolipid metabolism. Traditional research has focused on individual components, but recent evidence suggests that they may exert synergistic effects mediated by the gut microbiota [1,2]. This review systematically summarizes the mechanisms by which GPS and ginsenosides cooperatively regulate glucolipid metabolism via the gut–organ axis. The gut–organ axis is defined as the bidirectional communication network linking the gut microbiota (via its metabolites, such as short-chain fatty acids and succinate) to distal organs (liver, pancreas, and brain). The available evidence indicates that GPS act as prebiotics, modulating gut microbiota composition, promoting short-chain fatty acids (SCFAs) production, and enhancing the biotransformation of ginsenosides [1,6]. Ginsenosides are metabolized by the gut microbiota into highly active metabolites (e.g., Compound K) and differentially enrich Proteobacteria and succinate [2,8]. GPS and ginsenosides jointly activate intestinal gluconeogenesis (IGN) through complementary pathways (SCFAs via FFAR2/FFAR3, succinate via SUCNR1), and the resulting portal vein glucose signal further influences systemic energy homeostasis via the gut-liver and gut-brain axes [2,8]. This "divergent microbiota modulation–convergent target engagement" synergistic pattern provides a mechanistic explanation for the multi-component metabolic regulation of ginseng and offers a new mechanistic perspective for the health management of metabolic diseases.

Keywords: Ginseng polysaccharides (GPS); Ginsenosides; Gut microbiota; Intestinal gluconeogenesis (IGN); Glucolipid metabolism

1. Introduction

Panax ginseng C.A. Meyer has long been used in traditional medicine to maintain metabolic balance and has attracted considerable attention in modern weight management and metabolic health [2,3]. Ginseng polysaccharides (GPS) and ginsenosides are two major classes of bioactive constituents of ginseng, both showing potential to regulate glucolipid metabolism [1,3]. Although GPS are large biological macromolecules that cannot be directly absorbed across the intestinal mucosa, they exhibit significant bioactivity by modulating the gut microbiota as prebiotics [1,2]; ginsenosides, in contrast, require gut-microbiota-mediated biotransformation to exert their pharmacological effects [2].

Recent studies have revealed that the gut microbiota is a critical link connecting herbal components to host health [2,4]. There is a bidirectional regulation between ginseng constituents and the gut microbiota: the microbiota metabolize ginsenosides into more active compounds, while GPS act as prebiotics to shape microbial composition [1,2]. Importantly, emerging evidence suggests that GPS and ginsenosides may produce synergistic effects through gut-microbiota-mediated pathways [1,2,6]. Existing reviews have largely focused separately on the prebiotic effects of GPS [1] or the microbial biotransformation of ginsenosides [4,6]; none have systematically integrated the synergistic regulation of both as a central theme. Moreover, Luo et al. (2025) [2] recently reported the ground-breaking finding that ginseng polysaccharides and ginsenosides cooperate to combat obesity via divergent microbial pathways, providing a key experimental basis for re-evaluating the "whole-component" mode of action of ginseng.

A meta-analysis including 20 randomized controlled trials (clinical meta-analysis evidence) confirmed that supplementation with total ginseng extract significantly reduces fasting plasma glucose, total cholesterol, the homeostatic model assessment of insulin resistance (HOMA-IR), and interleukin-6 levels in individuals with prediabetes and type 2 diabetes mellitus [3]; however, this evidence comes from whole extracts and cannot be directly extrapolated to pure GPS or ginsenoside combinations. Currently, there is no systematic review that explicitly takes "GPS–ginsenoside synergy" as its main line, and most mechanistic studies are still confined to animal models, leaving a large gap for clinical translation. In particular, there is a lack of systematic evaluations of specific polysaccharide structures combined with specific ginsenoside monomers, the quantitative contribution of intestinal gluconeogenesis (IGN) to human metabolic regulation remains unclear, and no microbiota-stratified personalized ginseng intervention study has been reported. This review, from the perspective of the gut–organ axis, systematically synthesizes the mechanisms by which GPS and ginsenosides synergistically regulate glucolipid metabolism and discusses their potential applications and limitations.

2. Metabolic Regulation of Ginseng Polysaccharides and Ginsenosides and Evidence for Their Synergy

2.1 Prebiotic Effects and Metabolic Regulation of GPS (Animal Evidence)

Common extraction methods for GPS include hot-water extraction, ethanol precipitation, and column chromatography. Representative structures (including alkali-soluble components) have been systematically characterized by spectroscopic and chromatographic methods, including an α-(1→4)-linked galacturonic acid backbone and arabinose-rich side chains, with molecular weights ranging from 2.5 to 1800 kDa [1,7]. Animal studies have shown that GPS significantly improve insulin resistance, promote insulin secretion, and inhibit high-fat-diet-induced weight gain (animal evidence) [2,6].

As prebiotics, GPS selectively enrich beneficial bacteria such as Bacteroides, Bifidobacterium, Lactobacillus, Roseburia, and Akkermansia [1,6]. The SCFAs produced by GPS fermentation (mainly acetate, propionate, and butyrate) regulate energy metabolism via FFAR2/GPR43 and FFAR3/GPR41 receptors and maintain intestinal barrier integrity by enhancing the expression of tight junction proteins (e.g., occludin, claudin-1, ZO-1) [1,2,4,5].

2.2 Metabolic Transformation and Microbiota Interplay of Ginsenosides

Ginsenosides are generally divided into protopanaxadiol (PPD) type (e.g., Rb1, Rd, Rg3, Compound K) and protopanaxatriol (PPT) type (e.g., Rg1, Re, Rf) [2]. Their oral bioavailability is low (<20%), and they require gut-microbiota-mediated deglycosylation: Rb1 → Rd → F2 → Compound K → PPD [2,6]. Bacterial β-glucosidase plays a key role in this process [1,2,6]. Compound K is significantly more bioactive than its parent compounds [2,6].

At the same time, ginsenosides can also reciprocally modulate the microbiota: they enrich Proteobacteria such as Sulfurospirillum halorespirans and upregulate genes involved in succinate production [2,8]. In vitro cell experiments demonstrated that a 9:1 combination of ginsenosides Rb1 and Rg3 maximally promotes adipocyte differentiation and enhances insulin signaling (in vitro evidence) [9]. Furthermore, a combination of polysaccha-

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rides and ginsenosides from American ginseng (Panax quinquefolius) has been reported to ameliorate cyclophosphamide-induced intestinal immune disorders and barrier dysfunction by modulating the gut microbiota [10]. A recent study also found that ginsenoside Rg1 activates brown adipose tissue to counteract high-fat-diet-induced obesity by regulating the gut microbiota and bile acid composition [12].

2.3 Direct Synergistic Evidence (Animal Evidence)

In a diabetic rat model, co-administration of GPS and ginsenoside Rb1 markedly enhanced the hypoglycemic effect. Specifically, after 15 days of GPS administration, the gut microbiota were isolated and incubated in vitro with Rb1 for 8 hours; the conversion rate of Compound K increased from 14.0% to 86.7%. Concomitantly, GPS significantly elevated fecal β-glucosidase activity (animal evidence) [6]. In addition, GPS optimized the metabolic pathway of ginsenosides by suppressing intermediate metabolites and improved the absorption of ginsenosides (increased Cmax and AUC) [1,6]. These observations provide direct experimental support for GPS–ginsenoside synergy.

3. Gut-Microbiota-Mediated Synergistic Mechanisms

3.1 GPS Promote Ginsenoside Biotransformation

GPS accelerate the deglycosylation of ginsenosides by increasing the activity of β-glucosidase in the gut microbiota, thereby generating highly active secondary metabolites such as Compound K [1,6]. This process not only raises the absorption rate of ginsenosides but also enables more bioactive metabolites to reach target tissues. Meanwhile, the SCFAs produced by GPS fermentation may further create a favourable microenvironment for ginsenoside metabolism (e.g., by maintaining epithelial barrier integrity and modulating luminal pH), although this causal chain awaits direct validation.

3.2 Divergent Microbiota Modulation by GPS and Ginsenosides

On the basis that GPS promote ginsenoside biotransformation, the parent ginsenosides and their highly active metabolites (e.g., Compound K) can also reciprocally shape the microbial niche, establishing a two-way crosstalk. Existing studies have revealed divergent effects of GPS and ginsenosides on the gut microbiota [2,8]:

GPS: Enrich Bacteroidetes (e.g., Bacteroides stercorirosoris) and upregulate SCFA-synthesis-related genes (K00625, K00925) as well as IGN-related genes (K01678, K00024, K01596).

Ginsenosides: Favour Proteobacteria (e.g., Sulfurospirillum halorespirans) and upregulate succinate-production genes (K18118, K00100, K18122) and IGN-related genes (K18118, K00278).

Table 1. Differential modulation of gut microbiota by ginseng polysaccharides (GPS) and ginsenosides.

Characteristic	Ginseng Polysaccharides (GPS)	Ginsenosides
Enriched Phylum	Bacteroidetes	Proteobacteria
Key Genus	Bacteroides stercorirosoris	Sulfurospirillum halorespirans
Primary Metabolites	Acetate, Propionate, Butyrate (SCFAs)	Succinate
Upregulated Genes	K00625, K00925, K01678	K18118, K00100, K00278
Key Receptors	FFAR2 (GPR43), FFAR3 (GPR41)	SUCNR1
Primary Effects	Energy metabolism, Barrier integrity, IGN activation	Succinate-driven IGN activation

Both components collectively optimise the overall microbial community structure, suggesting that different chemical constituents of the same herb can target complementary microbial populations [2,8]. Red ginseng extract combined with dietary fibre increases the abundance of beneficial bacteria such as Lactobacillus, Roseburia, and Akkermansia and enhances SCFA metabolism and lipid metabolism [5].

Moreover, SCFAs produced by GPS (especially butyrate) reduce intestinal permeability by strengthening tight junction proteins (occludin, claudin-1, ZO-1), thereby decreasing the translocation of lipopolysaccharide (LPS) into the systemic circulation [1,6]. Reduced LPS translocation downregulates the activation of Toll-like receptor 4 (TLR4)/nuclear factor-κB (NF-κB) inflammatory signalling in the liver and adipose tissue, ameliorating chronic low-grade inflammation and insulin resistance [2,4]. This barrier-protective effect is independent of the IGN path-

way and provides a parallel upstream mechanism for the GPS–ginsenoside synergistic improvement of glucolipid metabolism.

3.3 Convergent Activation of Intestinal Gluconeogenesis by Metabolites via Distinct Receptors

SCFAs and succinate initiate intracellular signalling cascades (e.g., cAMP/PKA or Ca^{2+} pathways) through different cell-surface receptors and subsequently upregulate the expression and activity of key IGN enzymes, such as PEPCK and G6Pase [2,8]. SCFAs primarily act on FFAR2/GPR43 and FFAR3/GPR41, whereas succinate acts mainly through succinate receptor 1 (SUCNR1). It should be noted that the direct causal evidence for FFAR2/FFAR3→IGN and SUCNR1→IGN currently comes mainly from gene-expression association studies and pharmacological agonist/antagonist experiments; the complete signal transduction cascade from receptor activation to upregulation of IGN enzymes still requires further validation. Moreover, the receptor system for SCFAs is not limited to FFAR2/FFAR3 (e.g., HCAR2 also participates), but the available evidence consistently indicates that both pathways contribute complementarily to IGN enhancement. In animal models, activated IGN produces glucose within intestinal epithelial cells, which is released into the portal vein via basolateral glucose transporters. The portal vein system senses this signal and transmits it to the liver and brain, thereby regulating whole-body energy homeostasis [2,8].

Notably, succinate displays a dual effect in the metabolic regulation of extra-intestinal tissues (especially adipose tissue). On the one hand, in the obese state, SUCNR1 expression in adipose tissue macrophages is downregulated, leading to attenuated anti-inflammatory function and indirectly manifested as enhanced pro-inflammatory signals (Keiran et al., 2019) [13]; on the other hand, succinate can also promote brown adipose tissue thermogenesis via succinate dehydrogenase (SDH) to counteract obesity (Mills et al., 2018) [14]. Thus, the ultimate net effect of the extra-intestinal succinate–SUCNR1 axis depends on the target cell type and the metabolic state, and remains to be further elucidated.

4. Gut–Organ Axis Integration of Systemic Glucolipid Metabolism

4.1 Coordination of the Gut–Pancreas, Gut–Liver, and Gut–Brain Axes

Based on the metabolic signals generated at the third level of the three-tier cascade (target convergence), i.e., portal glucose, GLP-1, and SCFAs, the following three gut–organ axes mediate systemic effects [1,2,3,5]:

· Gut–pancreas axis: Stimulates intestinal L-cells to secrete glucagon-like peptide-1 (GLP-1) and peptide YY (PYY). GLP-1 acts via the circulation on the GLP-1 receptor of pancreatic β-cells, activating the cAMP/PKA pathway to promote glucose-dependent insulin secretion; PYY slows gastric emptying and suppresses appetite.

Gut–liver axis: Portal vein glucose signals are sensed by hepatic metabolic sensors, which inhibit hepatic gluconeogenesis (downregulating G6Pase and PEPCK) and achieve a reassignment of gluconeogenesis from the liver to the intestine. This IGN-dominated gut–liver cooperation not only avoids excessive hepatic glucose production but also improves whole-body insulin sensitivity. At the same time, SCFAs (especially butyrate) reach the liver via the portal vein and regulate the expression of lipogenic genes by inhibiting histone deacetylases (HDACs).

Gut–brain axis: SCFAs and GLP-1 activate the nucleus tractus solitarius (NTS) in the brainstem via vagal afferent fibres, which in turn modulates the activity of orexigenic (AgRP/NPY) and anorexigenic (POMC) neurons in the hypothalamic arcuate nucleus, suppressing appetite and reducing energy intake.

GPS and ginsenosides translate their locally generated divergent signals in the gut into systemic glucolipid metabolic effects precisely through these gut–organ axes.

4.2 Construction and Limitations of a Conceptual Framework

Based on the available evidence, a three-tier cascade conceptual framework for "GPS–ginsenoside synergy" can be constructed (Figure 1):

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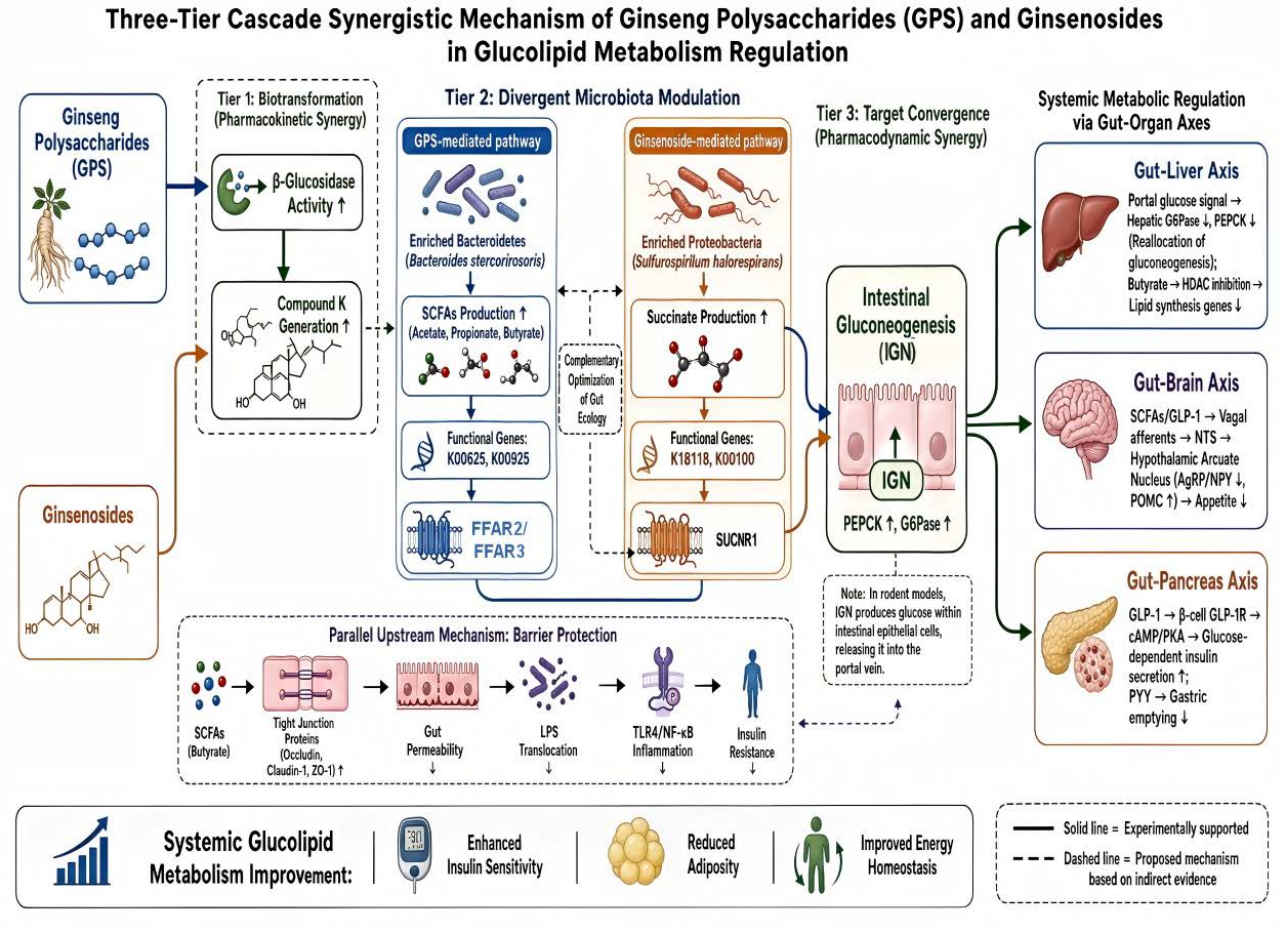

Figure 1. Schematic illustration of the three-tier cascade synergistic mechanism of ginseng polysaccharides (GPS) and ginsenosides in glucolipid metabolism regulation.

1. Biotransformation tier: GPS upregulate β-glucosidase activity and promote the conversion of ginsenosides into highly active metabolites [1,6].
2. Microbiota-modulation tier: GPS enrich Bacteroidetes/SCFAs, while ginsenosides enrich Proteobacteria/succinate; together they optimise the microbial ecology [2,8].
3. Target-convergence tier: SCFAs (via FFAR2/FFAR3) and succinate (via SUCNR1) jointly activate IGN, which then regulates whole-body energy homeostasis through the portal vein–gut–liver/gut–brain axes [2,8].

This framework is a tentative model based on current animal and in vitro data. Direct clinical evidence supporting each tier is still lacking, especially the quantitative contribution of portal glucose signalling in humans remains to be explored. Nonetheless, the framework provides an integrative conceptual model for understanding the multi-component metabolic regulation of ginseng: i.e., through divergent modulation of the gut microbiota and their metabolites, the two components eventually converge on the same metabolic pathway to synergistically improve glucolipid metabolism.

5. Conclusions and Perspectives

5.1 Key findings

This review systematically synthesises the mechanisms by which GPS and ginsenosides synergistically regulate glucolipid metabolism via the gut–organ axis. The main conclusions are as follows: GPS act as prebiotics, modulating gut microbiota composition, promoting SCFA production, and enhancing ginsenoside biotransformation [1,6]; ginsenosides are metabolized by the microbiota into highly active compounds while differentially enriching Proteobacteria/succinate [2,8]; both components jointly activate IGN through complementary receptor pathways FFAR2/FFAR3vs.SUCNR1 , which in turn influences systemic energy homeostasis via the gut–liver and gut–brain axes [2,8]. This "divergent microbiota modulation–convergent target engagement" synergistic model breaks away from previous studies that focused on single components and provides a mechanistic new perspective for understanding multi-component metabolic regulation of

ginseng.

5.2 Limitations

Currently, most evidence originates from animal models and in vitro experiments, and direct clinical evidence for GPS–ginsenoside synergy remains extremely limited. The high-quality clinical meta-analysis [3] used total ginseng extract and cannot be directly extrapolated to pure GPS or ginsenoside combinations. Furthermore, the structural complexity of GPS, the diversity of ginsenosides, and inter-individual variations in gut microbiota pose challenges for standardisation and personalised applications. The dual effects of the succinate–SUCNR1 axis (thermogenesis vs. pro-inflammation) highlight that its metabolic outcome is highly dependent on the physiological context [13,14], and future studies should clarify the net contribution of succinate under different metabolic states. Inconsistent regulation of specific bacterial genera (e.g., Akkermansia) by GPS across different studies may be related to different disease models and polysaccharide structures. Asian ginseng [2,6] and American ginseng [10] may also exhibit species-specific differences in the microbial targets of polysaccharide–ginsenoside synergy.

5.3 Future directions

Future research should focus on the following issues: (1) randomised controlled trials that use "specific GPS + specific ginsenoside" combinations to determine the dose-response relationship, optimal ratio, and target population; (2) quantitative dissection of the contribution of IGN to whole-body energy metabolism using multi-omics approaches (metagenomics, metabolomics); (3) development of microbiota-stratified personalised ginseng health management strategies; (4) establishment of quality markers, taking into account the impact of processing methods (e.g., sulfur fumigation [11]) on polysaccharide activity; (5) optimisation of dosage forms, doses, and administration regimens for clinical translation; and (6) establishment of translational bridging strategies from in vitro/animal synergistic doses to clinically feasible doses, including population pharmacokinetic modelling and physiologically based pharmacokinetic (PBPK) simulations. These studies will provide a scientific foundation for the precise health management of metabolic diseases using ginseng.

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