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# Harnessing Synthetic Biology for Functional Metabolite Enhancement in *Panax ginseng*

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**Abstract** This study summarizes the new progress in ginseng metabolism research in recent years, including the analysis of metabolic pathways, the mining of functional genes, and the application of multi-omics in metabolic regulation. It introduces several commonly used methods, such as CRISPR/Cas9 gene editing, metabolic pathway modification, protein engineering, and fermentation condition optimization. These methods not only increased the yield of natural metabolites but also helped create some new derivatives. This study also discussed the current difficulties, such as the complexity of metabolic pathways, insufficient genetic resources, and the challenges when the achievements are industrialized. This study aims to provide ideas and practical references for the molecular improvement and industrial application of ginseng.
**Keywords** Ginseng (*Panax ginseng*); Synthetic biology; Functional metabolites; Ginsenoside; Metabolic engineering

## 1 Introduction

Ginseng (*Panax ginseng*) has long been known as the “King of Herbs” and has a long history of application in traditional East Asian medicine. Its root is the main medicinal part and is widely used to enhance immunity, delay aging, fight cancer, and improve cardiovascular and metabolic diseases, etc. A large number of basic and clinical studies have confirmed these efficacy (Park et al., 2021). However, due to the scarcity and unsustainability of wild ginseng, artificial cultivation and modern biotechnology have become the main ways to guarantee the medicinal value and industrial development of ginseng (Xu et al., 2023).

The medicinal effects of ginseng mainly come from a variety of active metabolites, including ginsenosides, polysaccharides and polyphenols. Among them, ginsenosides are the most representative, having anti-inflammatory, antioxidant, anti-tumor, neuroprotective and metabolic regulating effects (De Oliveira Zanuso et al., 2022). Polysaccharides have been found to have significant immunomodulatory and anti-tumor effects (Song et al., 2018). Polyphenols have attracted attention due to their antioxidant and cardiovascular protective functions (Park et al., 2021). The content and composition of these metabolites not only determine the medicinal value of ginseng, but also directly affect its application potential in fields such as food, health products and medicines (Eom et al., 2018; Xu et al., 2023).

This study summarizes the biosynthetic pathways and regulatory mechanisms of the main functional metabolites of ginseng, introduces the latest progress of synthetic biology in increasing the content of active components such as ginsenosides, polysaccharides and polyphenols, and also discusses the opportunities and challenges for achieving efficient production of active metabolites of ginseng through genetic engineering, metabolic engineering and smart agriculture in the future. This research aims to provide theoretical support and technical references for the molecular improvement and industrial utilization of active components in ginseng.

## 2 Functional Metabolites in *P. ginseng*

### 2.1 Ginsenosides: diversity, biosynthetic pathways, and pharmacological significance

Ginsenosides are the most studied and important active components in ginseng and belong to the triterpenoid saponins. More than one hundred monomers have been identified so far, mainly divided into two types: dammarane type (including protopanaxadiol-type PPD and protopanaxatriol-type PPT) and oleanane type (Jiang

et al., 2024). There are mainly two synthetic pathways for them: one is the mevalonic acid (MVA) pathway in the cytoplasm, and the other is the methylerythritol phosphate (MEP) pathway in the plastid. The entire process involves more than twenty enzymatic reactions (Liu et al., 2023). The pharmacological effects of ginsenosides are very extensive, including anti-inflammatory, anti-tumor, cardiovascular protection, anti-fatigue and immune regulation, etc. (Jiang et al., 2024). For example, PPT-type saponins can significantly inhibit the activation of NLRP3 inflammasomes, thereby exerting anti-inflammatory effects (Jiang et al., 2020).

### 2.2 Other metabolites: polysaccharides, flavonoids, and minor compounds

In addition to saponins, ginseng also contains polysaccharides, flavonoids and other components. Ginseng polysaccharides can regulate immunity and have antioxidant effects. Enzymatic extraction can also enhance the immune stimulation effect (Song et al., 2018). Flavonoids and some other minor components, such as alkaloids, volatile oils, fatty acids, etc., also play auxiliary roles in anti-inflammation and antioxidation (Morshed et al., 2023). In addition, researchers also discovered novel indole alkaloids in it, which made the chemical composition of ginseng more diverse (Vu et al., 2023).

### 2.3 Current limitations in natural metabolite yield and stability

Although there are many types of ginseng metabolites, the problems of yield and stability remain prominent. Firstly, ginseng has a long growth cycle and high requirements for climate and soil. Therefore, the output of active components such as saponins is limited and fluctuates greatly (Xu et al., 2023; Jiang et al., 2024). Secondly, the environment, varieties and cultivation methods all affect the composition and content of metabolites (Yoon et al., 2022). Furthermore, saponins have a low absorption rate in the human body and are easily decomposed by intestinal microorganisms, which will reduce their bioavailability and efficacy (Mi et al., 2023; Wang et al., 2023). The extraction and purification processes of polysaccharides can also affect their structure and activity (Song et al., 2018). These issues have made synthetic biology the main approach to enhancing the yield and stability of functional components in ginseng.

## 3 Synthetic Biology Tools for Metabolite Engineering

### 3.1 Genome editing technologies: CRISPR/Cas, TALENs, ZFNs

Genome editing technology has brought new opportunities to ginseng metabolite engineering. The CRISPR/Cas9 system has been applied in ginseng to knock out or regulate key metabolic genes, thereby significantly increasing the production of some saponins, such as Rg3. Studies have shown that after knocking down the *CYP716A53v2* gene, the synthetic flux of the original ginsenoside Rg3 was significantly enhanced. Combined with other metabolic engineering methods, the yield of Rg3 was more than 21 times higher than that of the wild type (Yao et al., 2022). Although TALENs and ZFNs are also useful in other plants, research on ginseng is still scarce and may be expanded in the future.

### 3.2 Synthetic promoters, transcriptional regulation, and metabolic switches

The design of synthetic promoters and transcription factors also provides new approaches for regulating the metabolic genes of ginseng. For instance, WRKY-like transcription factors (PgWRKY4X) can activate the transcription of squalene epoxidase (PgSE), thereby significantly promoting the synthesis of saponins (Yao et al., 2020). In addition, researchers have designed metabolic switches and artificial regulatory elements, allowing the metabolic flow to be regulated according to external signals or inducers, which enables the accumulation of more target metabolites. These methods provide a molecular basis for directed synthesis and increasing the yield of ginsenosides.

### 3.3 Heterologous expression systems for metabolite biosynthesis (yeast, *E. coli*, plants)

Heterologous expression systems are the key for synthetic biology to achieve efficient production of ginseng metabolites. *Saccharomyces cerevisiae* is widely used to reconstruct the synthetic pathway of ginsenosides. By introducing multiple glycosyltransferases and key enzyme genes, the research has achieved the de novo synthesis of various saponins such as Rg2, Re, F1, Rh1, etc., and the yield can even reach the gram level (Figure 1) (Wang et al., 2020; Li et al., 2022a; Zhang et al., 2022). In addition, *E. coli* and plant cell culture systems are also

frequently used for the expression and validation of specific enzymes. Hairy root culture and transgenic root systems are also feasible. The saponin content of some transgenic roots even exceeds that of common cultivated roots (Binh et al., 2023).

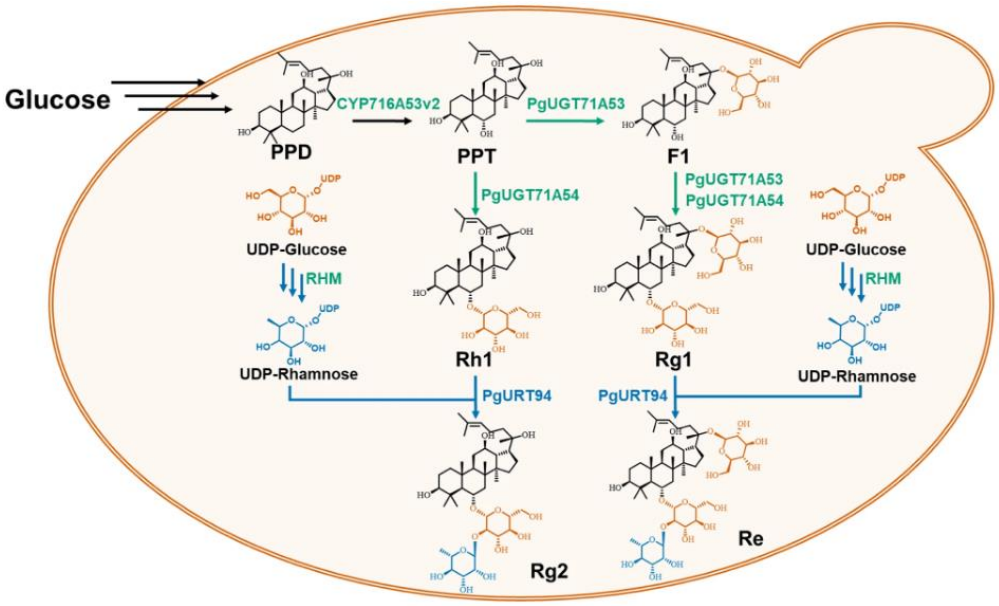


Figure 1 The proposed pathway for de novo biosynthesis of ginsenosides Rg2 and Re in engineered yeast strains (Adopted from Li et al., 2022a)

Image caption: Bluish green arrows represent glycosylation steps using UDP-glucose as a sugar donor, blue arrows represent the biosynthetic pathway of UDP-rhamnose and glycosylation steps using UDP-rhamnose as a sugar donor. Multi-step conversions were presented as multi arrows. Bluish green marked genes represented previous reported genes and the bule marked gene represented the identified one in this study. *PPD* protopanaxadiol, *PPT* protopanaxatriol (Adopted from Li et al., 2022a)

## 4 Omics-Guided Metabolic Engineering

### 4.1 Genomics and gene mining of biosynthetic enzymes

The analysis of the ginseng genome has laid the foundation for the study of functional metabolites. Whole-genome sequencing has revealed the complex tetraploid genomic structure of ginseng, annotating over 59000 genes. Researchers discovered important enzyme genes related to saponin synthesis, such as DDS and SQE, in the reconstruction of metabolic networks and revealed their evolutionary characteristics. These results provide targets for gene editing and synthetic biology (Kim et al., 2018; Yu et al., 2024). In addition, the amplification and diversity of the UDP-glycosyltransferase (UGT) family are closely related to the diversity of saponin structures. The functional verification and structural research of related genes have provided molecular basis for the directed synthesis of saponins.

### 4.2 Transcriptomics and co-expression networks for regulatory insights

Transcriptomics studies have revealed the dynamic changes and regulatory networks of key genes in the saponin synthesis pathway by analyzing gene expression profiles under different tissues, developmental stages and environmental conditions. The gene co-expression network helps researchers identify transcription factors and signaling pathways that may regulate saponin synthesis, deepening the understanding of the regulatory mechanism (Wei et al., 2024; Yu et al., 2024). For example, the combined analysis of transcriptome and metabolome can identify the gene modules related to saponin accumulation, which provides a reference for achieving multi-gene synergistic regulation in metabolic engineering (Kim et al., 2018; Yuan et al., 2023).

### 4.3 Metabolomics for pathway flux analysis and bottleneck identification

Metabolomics utilizes high-throughput mass spectrometry and other techniques to conduct systematic analysis of metabolites in different tissues, at different growth stages, and under different processing conditions of ginseng. Studies have revealed the dynamic changes of metabolites such as saponins and their flow distribution in

pathways (Kim et al., 2018; Yoon et al., 2022). Combined with metabolic flux analysis, the bottleneck links in the pathway can be located, and the accumulation of target metabolites can be increased by overexpression or knockout of key enzyme genes (Yao et al., 2022; Yuan et al., 2023). Furthermore, metabolomics can also compare metabolic differences under different environments, varieties and physiological states, providing data support for precise metabolic engineering design (Yoon et al., 2022).

## 5 Synthetic Pathway Design and Optimization

### 5.1 Reconstruction of ginsenoside biosynthetic pathways in microbial systems

In recent years, synthetic biology has promoted the efficient synthesis of ginsenosides in microorganisms. Researchers analyzed and reconstructed the complete pathways of ginsenosides (such as Rg2, Re, Ro, etc.) and achieved de novo synthesis starting from glucose in *Saccharomyces cerevisiae*. For instance, they identified and validated glycosyltransferases PgURT94, PgCSyGT1, PgUGT18, and PgUGT8, and modularly integrated them into *Saccharomyces cerevisiae* genome, resulting in the yields of Rg2 and Re reaching 1.3 g/L and 3.6 g/L, respectively (Li et al., 2022a; Zhang et al., 2022). This microbial factory provides a sustainable platform for the industrial production of saponins (Son et al., 2024).

### 5.2 Engineering rate-limiting enzymes for improved productivity

In the ginsenoside pathway, rate-limiting enzymes such as squalene synthase (SS), squalene epoxidase (SQE), β-amyrin synthase (bAS), CYP450 family and UDP-glycosyltransferase (UGT) play a key role in product accumulation. The content of target saponins can be significantly increased through methods such as gene overexpression, site-directed mutagenesis or CRISPR/Cas9 knockout of bypass enzymes. For example, overexpression of SS and downstream enzymes can increase triterpene saponins and phytosterols (Yao et al., 2022). In the semi-rational design and mutation experiments of glycosyltransferase Pq3-O-UGT2, its catalytic efficiency was enhanced. Combined with CRISPR knockout of the bypass enzyme CYP716A53v2, the yield of Rg3 was increased to 21 times that of the wild type (Yang et al., 2018; Yao et al., 2022). These methods provide feasible paths for the targeted production of specific saponins.

### 5.3 Systems biology approaches for balancing precursor supply and metabolite output

Systems biology integrates genomic, transcriptomic and metabolomic data to construct a global network for saponin synthesis. Studies have found that the distribution of precursor molecules (such as 2,3-oxidosqualene) in both the MVA and MEP pathways determines the accumulation of downstream products (Kim et al., 2018; Yu et al., 2024). Through metabolic flow analysis and model prediction, key genes (such as DDS, SQE) can be targeted and regulated to balance the supply of precursors and the output of downstream products, and reduce bottlenecks and by-products (Xu et al., 2023; Yu et al., 2024). These data also provide a basis for chassis cell design and multi-enzyme synergy, accelerating the development of high-yield strains (Xu et al., 2023; Son et al., 2024).

## 6 Case Study: Application of Synthetic Biology for Ginsenoside Enhancement

### 6.1 Research background and goals

Ginsenosides are the most important active components in ginseng and have functions such as anti-cancer, anti-oxidation and immune regulation. However, the traditional method of extracting saponins from ginseng is highly restricted. This is because ginseng has a long growth cycle, low yield, and is easily affected by the environment, making it difficult to meet the increasing market demand. The development of synthetic biology has provided a new approach for the efficient and sustainable production of saponins. The research objective is to achieve high-yield and diversified production of saponins and their derivatives by modifying metabolic pathways and optimizing host systems, and to promote their application in the pharmaceutical and health industry (Li et al., 2022b; Li et al., 2023; Qiu and Blank, 2023; Son et al., 2024).

### 6.2 Methodology: pathway engineering, host system selection, and validation

In synthetic biology, there are mainly three strategies for the production of ginsenosides. First, metabolic pathway engineering. Researchers reconstructed the saponin synthesis pathway by cloning and optimizing key enzyme genes (such as *DDS*, *CYP450*, *UGT*), and increased the accumulation of precursor substances (such as dammarenediol-II, protopanaxadiol) and target products (Wang et al., 2019; Yao et al., 2022). Second, host system

selection. *Saccharomyces cerevisiae* is the most commonly used host because it is convenient for genetic manipulation and its subcellular structure is also suitable for complex metabolic reactions. Meanwhile, researchers are also exploring new hosts such as *Chlamydomonas reinhardtii* (Figure 2) (Shi et al., 2021; Zhao et al., 2023). Third, system optimization and verification. Researchers enhanced metabolic flow and product yield through modular design, subcellular localization (such as directing key enzymes to lipid droplets), carbon source optimization (such as replacing glucose with glycerol), and protein engineering (such as directed evolution of UGT), and combined fermentation, extraction, and detection methods to validate the products (Shi et al., 2021; Yao et al., 2022; Zhang et al., 2024).

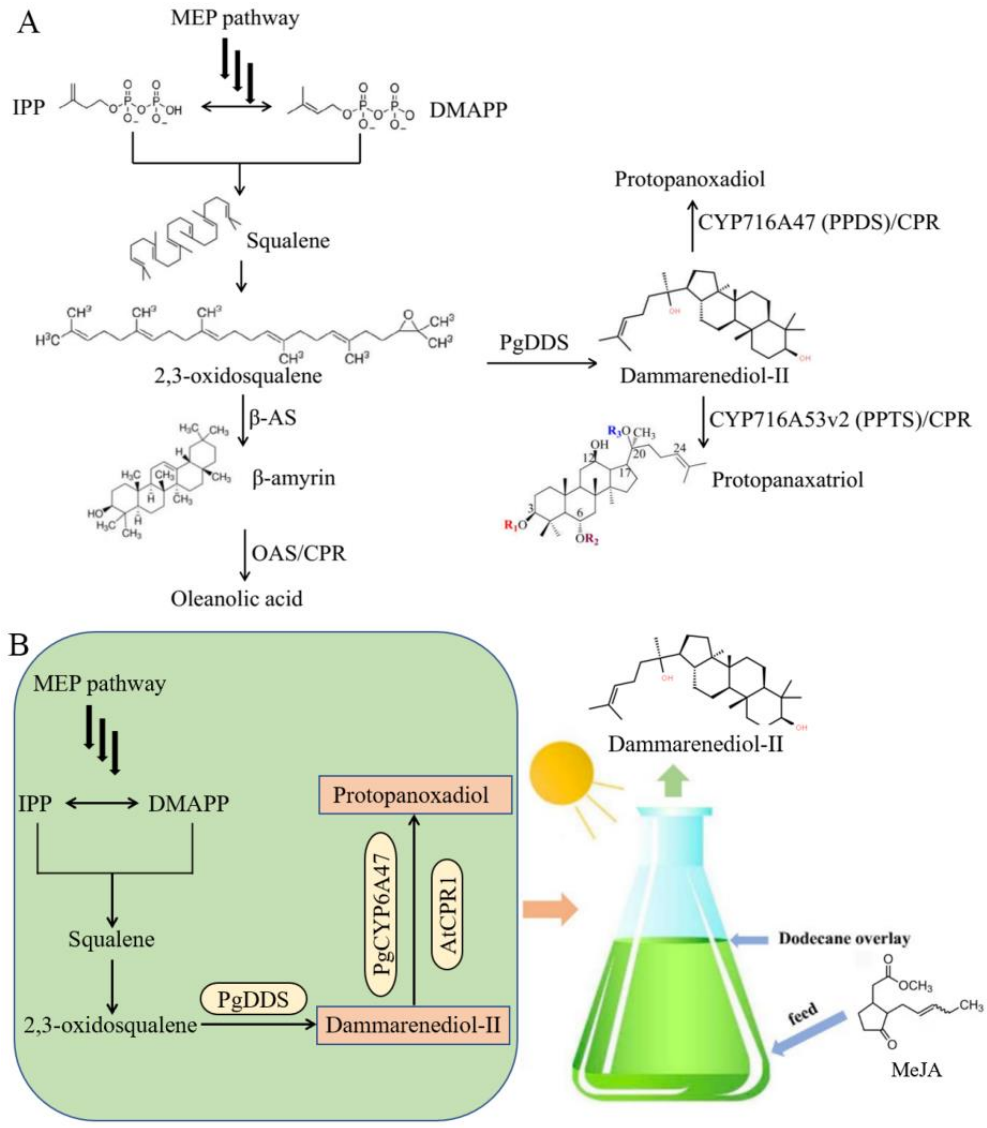


Figure 2 Biosynthesis pathways for ginsenoside production (A) and metabolic pathway design for the biosynthesis of dammarenediol-II and protopanoxadiol in engineered *Chlamydomonas reinhardtii* (B) (Adopted from Zhao et al., 2023)

Image caption: AtCPR1: *Arabidopsis thaliana* NADPH-cytochrome P450 reductase 1; β-AS: β-amyrin synthase; CPR: cytochrome P450 reductase; DMAPP: dimethylallyl diphosphate; IPP: isopentenyl pyrophosphate; MEP: 2-C-methyl-D-erythritol 4-phosphate; OAS: oleanolic acid synthase; PgDDS: *Panax ginseng* dammarenediol synthase; PgCYPCYP6A47: *Panax ginseng* Cyt P450 (CYP) enzyme (Adopted from Zhao et al., 2023)

### 6.3 Key findings: increased metabolite yield, new derivatives, and commercial implications

After multiple rounds of optimization, the yield of ginsenosides in *Saccharomyces cerevisiae* system has been increased from the milligarine level to the gram level. For example, the saponin yield in a single shake flask can reach 3.4 g/L. In the fermentation tank, the yields of saponins such as Rh2 and CK exceed 2 g/L, which is much

higher than that of the traditional extraction method (Wang et al., 2019; Qiu et al., 2024; Zhang et al., 2024). In addition, synthetic biology can not only efficiently produce natural saponins, but also synthesize non-natural saponins with novel structures and potential medicinal value through enzyme engineering and substrate modification (Dai et al., 2018; Shi et al., 2021). In terms of industrial application, microbial cell factories have provided a foundation for the industrialization of saponins due to their advantages such as low cost, sustainability and scalability. The development of high-yield systems and new saponins has opened up broad application prospects in fields such as medicine, health products and functional foods (Li et al., 2022b; Yao et al., 2022; Qiu and Blank, 2023; Son et al., 2024; Qiu and Blank, 2025).

## 7 Challenges and Research Gaps

### 7.1 Complexity of multi-gene biosynthetic pathways

The synthesis of active substances such as ginsenosides relies on many genes and complex metabolic networks. The genome of ginseng is large and there are many repetitive sequences. The families of related enzymes (such as UDP-glycosyltransferases and P450 enzymes) have a large number of members and significant functional differences. Therefore, it is very difficult to identify the key genes and reconstruct them in heterologous systems (Yang et al., 2018; Chopra et al., 2021). In addition, the expression levels of different enzymes, substrate selectivity and activity will all affect product accumulation. Bottleneck and bypass metabolisms in the pathway also make synthetic design more complex (Li et al., 2022a; Yao et al., 2022; Zhang et al., 2022).

### 7.2 Technical difficulties in stable transformation of *P. ginseng*

Ginseng itself is not easy to undergo genetic transformation. A stable transgenic system is difficult to establish, with low transformation efficiency and a long regeneration cycle. Although in vitro culture systems such as hairy roots and callus can be used for gene function verification and metabolic studies, there are still many limitations at the whole-plant level, such as strong genotype dependence, harsh culture conditions, and low regeneration rate (Zou et al., 2021; Xu et al., 2023; Zhu et al., 2024). Meanwhile, whether the expression of exogenous genes is stable and whether the copy number is controllable will also affect the accumulation of target metabolites (Yao et al., 2020).

### 7.3 Regulatory and biosafety considerations in synthetic biology applications

The application of synthetic biology in medicinal plants like ginseng often requires gene editing, the introduction of exogenous genes and the construction of microbial factories. However, these operations are subject to strict supervision and safety assessment. At present, there are no unified standards for the food and drug safety, environmental release risks and ethical issues of genetically modified ginseng and its metabolites, which limits industrialization (Yang et al., 2018; Chopra et al., 2021). In addition, the production of high-value products such as ginsenosides in microbial systems also involves issues of intellectual property rights, product traceability and market access, which also need to be further regulated (Li et al., 2022a; Zhang et al., 2022).

## 8 Future Perspectives

### 8.1 Integration of AI, machine learning, and computational modeling for pathway design

With the in-depth research on the ginseng genome and metabolic network, artificial intelligence (AI), machine learning (ML), and computational modeling have begun to play a significant role in synthetic biology. AI and ML can predict key enzymes and regulatory elements by analyzing large-scale omics data and infer their effects on metabolic flow, thereby helping to optimize the synthetic pathways of functional components such as ginsenosides (Kim et al., 2018). Modeling methods based on genomes and transcriptomes can also reconstruct complex metabolic pathways and identify appropriate regulatory targets, providing theoretical support for the efficient synthesis of novel or high-content saponins (Song et al., 2024). In the future, combining the automated design of AI with high-throughput experiments is expected to significantly accelerate the directional modification of functional metabolites of ginseng and the breeding of new varieties.

### 8.2 Synthetic consortia and bioreactor systems for large-scale metabolite production

In the field of metabolic engineering, synthetic biology has driven the development of microbial cell factories. *Saccharomyces cerevisiae* and engineered bacteria are often used as hosts. Through multi-enzyme co-expression

and optimization of key glycosyltransferases, researchers have achieved high-level production of various ginsenosides (such as Rg2, Re, Rg3, Rh2, etc.) in microorganisms, and the yield can even reach the gram level (Yao et al., 2022; Zhang et al., 2022). Meanwhile, the development of synthetic microbial communities and modular reactors also provides new methods for increasing yield and diversity, which can convert inexpensive substrates (such as glucose) into high-value-added saponins (Li et al., 2022a). In addition, the combination of bioreactors and transgenic hairy root systems also provides a feasible approach for the large-scale production of ginseng active substances in vitro (Binh et al., 2023; Xu et al., 2023).

### 8.3 Prospects for next-generation functional foods and pharmaceuticals from *P. ginseng*

Synthetic biology can not only increase the yield of ginsenosides, but also provide a basis for the development of new functional foods and drugs. By regulating the structure and content of saponins, high-value products with anti-cancer, immunomodulatory or antioxidant effects can be developed specifically (Yao et al., 2022). In addition, microbial transformation and enzymatic modification can further enrich the structure and activity of ginseng components, providing resources for the development of health foods and new drugs (Eom et al., 2018; Song et al., 2018). In the future, if synthetic biology, AI design and mass manufacturing are combined, ginseng is expected to become an important source of personalized nutrition and precision medicine (Li et al., 2022a).

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## Conflict of Interest Disclosure

The authors affirm that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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