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Review Article

The history, beneficial ingredients, mechanism, processing, and products of *Panax ginseng* for medicinal and edible value

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Abstract: *Panax ginseng* has been used as a superior herb in traditional Chinese medicine (TCM) for at least 2,000 years. With its outstanding effects of nourishing, tranquilizing, and benefiting the mind, it has been traditionally used as an herbal remedy for a variety of ailments, such as physical weakness, thirst, or insomnia with palpitations. At the same time, it has also been used as a tonic ingredient in the daily diet of the Chinese, and various kinds of supplements made from it have been used to prolong longevity. This review focuses on the application history, current research progress (2004−2023), functional material basis and product development of *P. ginseng* as a "dual-use substance for medicine and food", and the pharmacological effects of its components on cancer, skin wound, thrombosis, inflammation, neurological disorders, etc. It also emphasizes the impact of processing technology on the nutritional and pharmacological effects of *P. ginseng* and reports the trends and challenges of its future research and development.

Keywords: *Panax ginseng*; ingredients; nutrition; medicine; processing; product

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1 Introduction

"Dual-use substances for medicine and food" are natural substances that combine medicinal and edible functions, and in which the medicinal substances have no toxic effects on the body and can be consumed for a long time. Chinese medicines are an important resource of "dual-use substance for medicine and food", which have been recognized over time through abundant production experience. Such herbal medicines are not only used as drugs but can also be used as part of daily diets or as functional foods. At the present age, subfertility and population aging increase the probability of a wide range of chronic diseases and pose a great threat to human health. Therefore, health services must urgently refocus on prevention as a primary strategy, integrating traditional Chinese medicine (TCM) to proactively address health issues. There is an urgent need to shift the medical paradigm from "treating existing diseases" to "preventing diseases". The therapeutic potential of TCM in the treatment of chronic and intractable diseases is increasingly recognized globally[1]. A significant aspect of this practice is the use of medicinal and dietary resources derived from the same origin, which serve as unique health resources within the framework of TCM and dietary health[2-4].

Panax ginseng C.A. Meyer, a member of the Panax genus within the Araliaceae family, was first documented in *Shen Nong's Herbal Classic*[5]. *P. ginseng* is primarily produced in northeastern China, although it and its related species are also found in East Asia, Central Asia, and North America. Based on various sources and cultivation methods, it can be categorized into wild ginseng, forest ginseng, garden ginseng, and other varieties. Typically, it is processed into products such as red ginseng, black ginseng, and sugar ginseng. While the roots and rhizomes are the main medicinal parts, the leaves and fruits are increasingly being utilized for their beneficial properties. Esteemed for its capacity to tonify vital energy, nourish the spleen and lungs, generate bodily fluids, and promote mental clarity, *P. ginseng* has a vital position and is regarded as a representative of TCM. Nowadays, it has emerged as one of the best-selling natural products globally[6]. Beyond its traditional medicinal applications, *P. ginseng* is widely utilized as a key ingredient in health products, functional foods, and cosmetics[7]. It referred to as the foremost of the 'Three Treasures of Northeast China,' *P. ginseng* has been the subject of extensive research regarding its nutritional and medicinal properties since ancient times, demonstrating its comprehensive utility in both

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medicinal and dietary contexts (Fig. 1).

Modern research on *P. ginseng* primarily focuses on its material basis, initiating with the isolation and identification of saponin compounds, commonly referred to as ginsenosides. The first ginsenoside was isolated from American ginseng by Garrigues in 1854, who named it "panaquillon"[8]. Currently, a variety of components, including saponins, polysaccharides, flavonoids, organic acids (esters), amino acids, sterols, and carbenes, have been identified in *P. ginseng* and related species. As of 2020, at least 200 distinct types of ginsenosides have been isolated and characterized, alongside the discovery of multiple polysaccharide substances[9]. Saponins and polysaccharides are recognized as the two principal categories of compounds that significantly contribute to the medicinal and nutritional properties of *P. ginseng*[10,11]. Various ginsenoside compounds are involved in regulating a range of physiological activities within the body[12-19]. Additionally, ginseng polysaccharides have garnered attention due to their substantial biological activity[20,21].

Despite significant advancements in understanding the material basis, pharmacological effects, mechanisms of action, and drug development associated with *P. ginseng*, research in this area continues to evolve. Recognized as both a medicinal and edible herb in TCM, recent investigations have increasingly focused on its nutritional value and functional food properties. However, there remains a notable scarcity of food products that incorporate *P. ginseng* as a primary ingredient, underscoring the necessity for further product development. This review aims to provide a comprehensive overview of the historical evolution, current research, and applications of *P. ginseng* as both a medicinal and edible herb, with an emphasis on its nutritional benefits as a food source and its therapeutic effects as a medicine. The objective is to offer insights into the exploration of the dual 'food' and 'medicine' value of *P. ginseng*.

2 Traceability of historical applications of *P. ginseng* and its processed products

2.1 Records of *P. ginseng* applications

The medicinal use of *P. ginseng* has a long-standing history in China, as evidenced by a plethora of medical texts from various dynasties. These writings offer valuable insights into the medicinal attributes, efficacy, and clinical implications of *P. ginseng*. The oldest Chinese herbal compendium, *Shen Nong's Herbal Classic*, delineates the diverse applications of *P. ginseng*[5]. This herb is renowned for nourishing organs, soothe the mind, alleviate palpitations, dispel negativity, enhance vision, stimulate cognitive function, and promote longevity. The book *Variorum of Shennong's Classic of Materia* stands out as the earliest herbal tome to document the growth patterns and physical appearance of *P. ginseng*[22], serving as a fundamental source for elucidating the origins of *P. ginseng* in subsequent eras. The *Catalogue of Famous Doctors*, a publication from the late Han Dynasty, notes that *P. ginseng* can quench thirst, enhance blood circulation, dissolve obstructions, and confer overall health benefits[23]. The renowned medical authority from the Tang Dynasty, Sun Simiao, incorporated 358 *P. ginseng*-based prescriptions in his work "*Urgent Prescriptions for a Thousand Treasures*", many of which continue to be utilized in modern times[24]. "*Compendium of Materia Medica*," authored by Li Shizhen, documented the use of *P. ginseng* in treating a range of deficiency syndromes in both men and women. These include fever, sweating, dizziness, headache, nausea, vomiting, malaria, diarrhea, frequent urination, dribbling, fatigue, internal injuries, and stroke, as well as heat stroke, paralysis, hematemesis, hemoptysis, uterine bleeding, and various conditions related to pregnancy[25]. Numerous ancient texts provide detailed accounts of *P. ginseng*'s origins, medicinal attributes, therapeutic effects, and clinical utilities. A synthesis of these records is presented in Table 1.

In addition to medicinal use, *P. ginseng* has also been used as a kind of food throughout Chinese history. Ancient Chinese physicians identified certain species that could serve both medicinal and nutritional purposes, referring to them as 'medicinal food homologous' or 'medicinal food dual-use'[26]. *P. ginseng* and its processed products exemplify TCM that possesses both therapeutic and edible qualities. Notably, *P. ginseng* is ranked among the highest in *Shen Nong's Herbal Classic*[5], signifying that ancient Chinese societies acknowledged ginseng as both a medicine and a food for an extended period. The medical and pharmaceutical historical documents cited previously provide

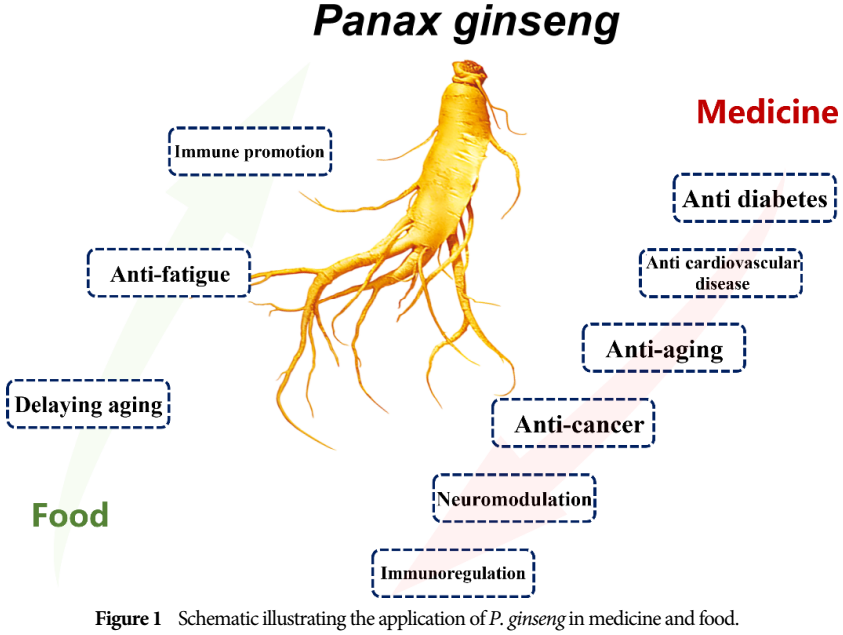

Figure 1 Schematic illustrating the application of *P. ginseng* in medicine and food.

Table 1 Overview of *P. ginseng* in TCM works across historical epochs

Dynasty	Classic	Record	Reference
Eastern Han	*Shen Nong's Herbal Classic*	Sweet and slightly cold in taste, it mainly nourishes the five organs, soothes the spirit, calms the soul, relieves fear, eliminates evil energy, improves eyesight, brings happiness, and enhances intelligence. Long-lasting taking leads to a lighter body and longer lifespan	[5]
Eastern Han	*Catalogue of Famous Doctors*	Treat colds in the gastrointestinal tract, chest and abdominal pain, chest, and rib fullness, and cholera vomiting, regulate the middle, quench thirst, promote blood circulation, through hard deposits, and make people unforgettable	[23]
Tang	*Treatise on Medicinal Properties*	The main treatment includes deficiency of *qi* in the five organs, exhaustion, and injuries, weakness and weakness, inability to eat due to vomiting, cessation of cholera, depression, nausea and vomiting, supplementation of the five organs and six viscera, and maintenance of the central nervous system. It also relieves phlegm in the chest, promotes the discharge of pus from pulmonary fistulas and epilepsy, prevents cold air reflux, and prevents eating due to typhoid fever. It is recommended for those who are deficient and have multiple dreams	[27]
Song	*Illustrated Classic of Materia Medica*	Let two people walk together, one with ginseng and the other empty, each walking about three to five miles. The one without ginseng will gasp heavily, while the one with ginseng will breathe freely	[28]
Jin	*Materia Medica of Decoction*	The taste is both sweet and warm, regulating the middle and nourishing *qi*, that is, replenishing the yang of the lungs and releasing the *yin* of the lungs. If one talks about replenishing the lungs, regardless of the coldness and heat of *yin* and *yang*, any deficiency of *qi* would be a mistake	[29]
Ming	*Compendium of Materia Medica*	Ginseng is used to treat all deficiency syndromes in men and women, including fever, sweating, dizziness, headache, nausea, vomiting, malaria, diarrhea, frequent urination, dribbling, fatigue, internal injury, stroke, heatstroke, paralysis, vomiting blood, coughing up blood, metrorrhagia, and various diseases before and after pregnancy	[25]

comprehensive information on the nutritional benefits and therapeutic effects of *P. ginseng*, underscoring its dual role as a source of nourishment and medicine.

2.2 The historical development of *P. ginseng* processing

The technique of processing is an essential pharmaceutical practice in TCM, and it can alter the medicinal properties and efficacy of the remedies. The understanding of *P. ginseng*'s processing methods among the Chinese has evolved significantly over time. Early historical documents primarily described basic cleaning steps, such as 'removing the reed'. However, over time, the method of steaming emerged, aimed at altering the medicinal properties of *P. ginseng*.

According to the *Lei Gong Treatise on Preparation*[30], which was written during the Southern and Northern Dynasties period, the method of processing ginseng to remove reeds was introduced, involving the filing of the four sides of the reed heads to assemble them into medicine. In the Ming Dynasty, The *Compendium of Materia Medica*[31] notes that "for cooked use, it is better to separate it from paper, bake it, or consume it with alcohol. To use it for roasting, and avoid iron utensils." This account provides a succinct overview of the methods for its processing and storing. Only with the recording in *Bencao Mengqi*[32] that "purple ginseng is large and slightly flattened" did it become widely circulated. The tradition of steaming red ginseng has endured through many generations. The preparation of red ginseng involves steps such as immersion, cleaning, sorting, steaming, drying, and air drying, all starting with raw ginseng. When compared to sun-dried ginseng, red ginseng includes the additional step of steaming[33]. And scientific research conducted by later generations has also proven that steaming can alter the medicinal properties of ginseng[34,35].

The medicating attributes of sun-dried ginseng are relatively cool, making it suitable for individuals with *qi* and *yin* deficiencies. Both white ginseng (WG) and sun-dried ginseng exhibit similar properties; however, red ginseng has warming medicinal qualities, rendering it more appropriate for those experiencing *qi* deficiency and *yang* weakness[36]. In various medical classics throughout history, discussions on the processing of *P. ginseng* have been documented and are consolidated in **Table 2.**

3 Visualization analysis of *P. ginseng*-related modern research hotspot map based on CiteSpace

3.1 Data and methods

3.1.1 *Data sources*

Data on English literature were sourced from the WOS Core Collection database in the Web of Science, with editions obtained from the Science Citation Index Expanded. The search criteria included the terms (Topic = (Ren Shen) or Topic = (Ginseng)), and the search period spanned from 2004 to 2023, resulting in the retrieval of 12,264 foreign documents. We restricted the document types to articles and reviews, selecting only those published in English. Following deduplication, a total of 10,098 valid documents were retained.

3.1.2 *Literature export and format conversion*

English literature was exported from the Web of Science in a 'plain text' format. The exported files were subsequently renamed to 'download_* *.txt.' Following this, the files were converted into a format compatible with CiteSpace 6.3.R1 for further analysis.

3.1.3 *Software operation and parameter setting*

To initiate the data analysis process using CiteSpace 6.3.R1 software, the first step involves importing the relevant data and creating a new project. The data source designated as Web of Science, with the time frame for analysis set from January 2004 to December 2023. Additionally, the years per slice configured to 1. When selecting node types for analysis, ensure that the keyword option is chosen, and proceed to analyze them in sequential order. For the analysis screening criteria, the g-index established at 3. To optimize the data, employ Pathfinder + Pruning Sliced Networks for pruning, and select 'All' for the term source. It is crucial to maintain all other settings at their default values as provided by the software system. By adhering to these steps and parameters, the data analysis process within CiteSpace software will be executed accurately and efficiently.

Table 2 Changes in *P. ginseng* processing methods and their implications

Dynasty	Classic	Processing Method	Reference
Eastern Han	*Fahrenheit Tripitaka*	Remove reed	[37]
the Northern and Southern Dynasties	*Lei Gong Treatise on Preparation*	Collect the dry in the shade, remove the four sides of the reed and the black head	[30]
Tang	*Medical Secrets of an Official*	Grind finely, slice	[38]
Song	*Prescription of peaceful benevolent dispensary*	Remove reeds first and grind. Only then can it be used as medicine. Not removing the reed will cause vomiting. Be cautious	[39]
Ming	*Bencao Mengqi*	Remove the reeds and stems, and cut thinly before frying	[32]
Qing	*Processing Guide*	Tao Hongjing said: Ginseng is prone to decay, but if it is sealed in a new container, it can last for years without breaking. If ginseng is frequently exposed to wind and sun, it is easy to thrive. However, it can be stored in a pot filled with sesame oil, soaked and dried, and then harvested alternately with ginseng. It can be sealed and stored for several years. One method is to dry it by sprinkling it with dust and ash, and it can also be stored in a can. Li Yanwen said: When ginseng is alive, it is always sunny, so it does not like to see the wind and sun. It is advisable to close the mouth when it is raw and when it is ripe. Bake it on paper or use it to moisten and heat it with wine, and avoid iron utensils	[40]

3.2 Trend analysis of *P. ginseng* publications in the past 20 years

The variations in the number of scholarly articles released within a particular discipline can somewhat reflect the changing trends in the degree of interest captured by researchers, alongside the breadth of inquiry and innovation in that area. The trend of publications related to *P. ginseng* in Web of Science core databases is shown in **Fig. 2**. The body of English literature related to *P. ginseng* has exhibited a consistent upward trajectory from 2004 to 2023, with only minor declines observed in 2014, 2020, and 2023 compared to the preceding years. Notably, there was a significant growth trend during the periods of 2008–2013 and 2020–2022, culminating in peaks in 2013 and 2022, respectively. This increase in the volume of published English literature over the past two decades indicates that both domestic and international scholars have maintained a sustained interest in the research value of *P. ginseng*, resulting in the international recognition of relevant research outcomes.

3.3 Co-occurrence and clustering analysis of keywords in English literature

3.3.1 *Keyword co-occurrence analysis*

Keywords represent highly summarized themes within the literature, and keyword co-occurrence analysis utilizes these keywords as network nodes to create a co-occurrence graph, which consists of nodes and connections following network pruning. Subsequent analysis of these nodes and connections is performed to gain a deeper understanding of the research landscape. Among the relevant information analyzed, frequency and betweenness centrality serve as two critical indicators for assessing the significance of keywords. A larger keyword node indicates a higher frequency of occurrence, while a thicker connection signifies that two keywords appear together more frequently in the same literature. High centrality reflects the importance of a keyword, which can, to a certain extent, indicate the research hotspots within the discipline. Employing 'Keyword' as the network node, CiteSpace 6.3.R1 was utilized to analyze the relevant literature included in this study. The resulting co-occurrence map of keywords is presented in **Fig. 3A**, with additional information on Chinese and English keywords provided in **Table 3**.

The co-occurrence analysis of keywords in English literature identified a total of 271 nodes and 934 lines. Among these, 14 keywords had a frequency of 500 or more. By integrating the graph with the keywords, a deeper analysis was performed on the information associated with the nodes. In the co-occurrence graph, the keywords exhibiting high centrality included *P. ginseng* (0.56), *in vitro* (0.15), expression (0.14), and identification (0.14).

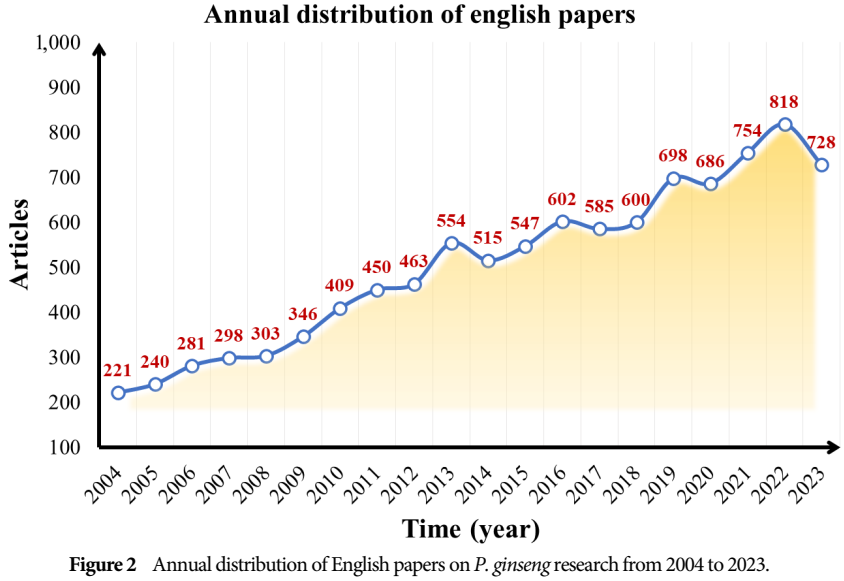

Figure 2 Annual distribution of English papers on *P. ginseng* research from 2004 to 2023.

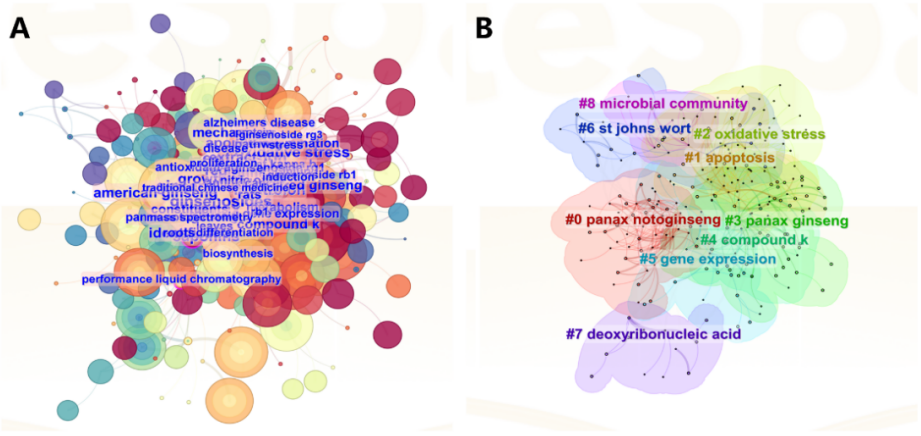

Figure 3 Keyword analysis of English literature on *P. ginseng*. (A) Co-occurrence network display of keywords; (B) Clustering network display of keywords.

Table 3 Information of high-frequency keywords in English literature on *P. ginseng*

No.	Keyword	Betweenness centrality	Number of publications/articles
1	*P. ginseng*	0.56	2,958
2	Ginseng	0.09	1,230
3	Ginsenosides	0.08	961
4	Expression	0.14	951
5	Activation	0.08	760
6	Saponins	0.11	747
7	Oxidative stress	0.08	739
8	Cells	0.07	704
9	*In vitro*	0.15	579
10	Extract	0.03	574

Furthermore, the research content in English literature predominantly emphasizes the extraction, separation, and activity studies of active ingredients in *P. ginseng*.

3.3.2 *Keyword clustering analysis*

The co-occurrence graph of keywords was analyzed using the log-likelihood ratio (LLR) algorithm to cluster closely related keywords from the relevant literature, resulting in the keyword clustering graph presented in **Fig. 3B**. This English literature keyword clustering map comprises 271 nodes and 943 connections, forming a total of 12 distinct clustering labels. The clustering module value, *Q*, is 0.440,0 (exceeding the threshold of 0.3), and the average contour value, *S*, is 0.764,2 (above the threshold of 0.7), indicating that the identified clustering network structure is significant and the results are reliable. The pharmacological research module includes clusters #1, #5, #6, #7, and others, while the component extraction and analysis module encompasses clusters #0, #2, #3, #4, #8, and more.

4 Multi-component material basis of *P. ginseng* for medicinal and edible purposes

Through bibliometric analysis, we found that the primary focus of ginseng research centers on two aspects: the material basis and the effect mechanism. Additionally, the multi-component composition of *P. ginseng* is a crucial foundation for its diverse biological effects as a 'dual-use' TCM. The chemical components of *P. ginseng*, such as ginsenosides, polysaccharides, volatile oils, vitamins, sterols, nucleotides, proteins, organic acids, and inorganic elements, form the nutritional and medicinal basis for its effects. Research has focused on ginsenosides, polysaccharides, and their values, with advancements in technology leading to the discovery of special active ingredients like Gintonin[41-44]. This has expanded our knowledge of *P. ginseng*'s chemical composition and potential benefits.

4.1 Saponins

Ginsenosides, the primary active ingredients found in *P. ginseng*, can be categorized into three main types based on their core structure: protopanaxadiol-type saponins (PPD), protopanaxatriol-type saponins (PPT), and oleanolic acid-type (OA) (**Fig. 4**). Examples of the PPD type include ginsenosides Rb1, Rc, and Rd, while the PPT type encompasses ginsenosides Re, Rf, and Rg1, and the OA type primarily consists of ginsenoside Ro[45]. Currently, the ginsenoside content serves as a crucial parameter for assessing the quality of *P. ginseng*. The representative components of various types of saponins are shown in **Table 4**[46-51]. During the processing of ginseng, there may be

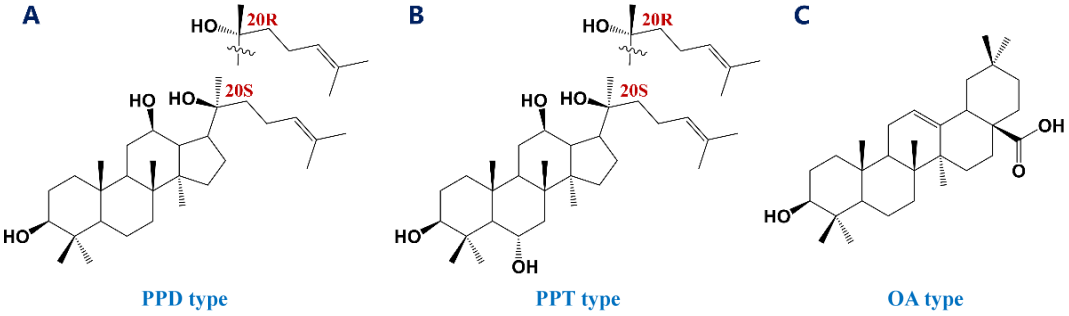

Figure 4 Main structural types of ginsenosides. (A) PPD; (B) PPT; (C) OA.

Table 4 Information for the representative components of ginsenosides newly isolated from *P. ginseng*

No.	Type	Trivial name	Molecular formula	Source	Reference
1	PPD	Ginsenoside Rb4	$C_{54}H_{92}O_{23}$	PG	[46]
2	PPD	Ginsenoside Rb5	$C_{60}H_{102}O_{28}$	PG	[46]
3	PPD	Ginsenoside Rs11	$C_{55}H_{92}O_{23}$	PG (root)	[47]
4	PPT	Ginsenoside Rg18	$C_{42}H_{72}O_{14}$	PG (root)	[47]
5	PPT	6-Acetyl Ginsenoside Rg3	$C_{50}H_{84}O_{20}$	6-Acetyl PG (root)	[47]
6	PPT	Dammar-24-ene-3*α*, 6*α*, 12*β*, 20S-tetraol (Ginsengenin-S1)	$C_{30}H_{52}O_4$	PG	[48]
7	Other	Ginsenoside Rg11	$C_{42}H_{70}O_{14}$	PG (root)	[49]
8	Other	12-*O*-Glucoginsenoside Rh4	$C_{42}H_{70}O_{13}$	PG (root)	[49]
9	Other	Ginsenoside Rh10	$C_{36}H_{62}O_8$	PG (root)	[49]
10	Other	Ginsenoside Re7	$C_{48}H_{82}O_{19}$	PG (root)	[51]
11	Other	Ginsenoside Rg12	$C_{42}H_{72}O_{15}$	PG (root)	[50]
12	Other	(20*S*, 22*S*)-Dammar-22,25-epoxy-3*β*, 12*β*, 20-triol	$C_{30}H_{52}O_4$	PG (root)	[51]
13	Other	6-*O*-[*α*-*L*-Rhamnopyranosyl-(1→2)-*β*-*D*-glucopyranosyl]-20-*O*-*β*-*D*-glucopyranosyl-dammarane-3*β*, 6*α*, 12*β*, 20*S*, 24*S*, 25-hexaol (ginsenoside S3)	$C_{48}H_{84}O_{20}$	PG	[48]
14	Other	6-*O*-[*α*-*L*-Rhamnopyranosyl-(1→2)-*β*-*D*-glucopyranosyl]-20-*O*-*β*-*D*-glucopyranosyl-dammarane-12-one-3*β*, 6*α*, 20*S*, 24*R*, 25-pentaol (ginsenoside S4)	$C_{48}H_{82}O_{20}$	PG	[48]

Note: PG: *P. ginseng*.

changes in the ratio of primary saponins to rare saponins due to chemical reactions such as glycosidic bond cleavage (**Fig. 5**). In recent years, phytochemical research has increasingly focused on identifying active compounds in parts of ginseng beyond the traditional medicinal sources, such as roots and rhizomes. Notably, a variety of new ginsenosides have been isolated and characterized from the flower buds[52, 53], feeds[54, 55], leaves, and stems[56-62] of the plant.

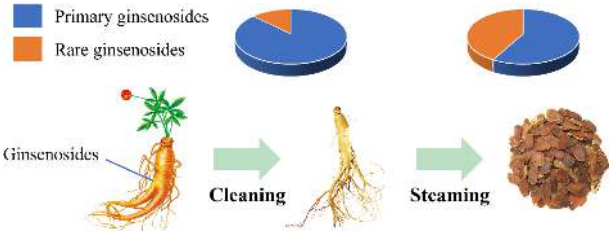

Figure 5 Changes in the amount of hospital level ginsenosides and rare ginsenosides in the processing of *P. ginseng*.

4.1.1 PPD

PPD is characterized by the presence of a trihydroxy-substituted dammarane skeleton at specific positions, namely C-3, C-12, or C-20. The structural framework of PPD-type saponins is defined by two primary characteristics. Firstly, there are preferred glycosylation sites located at positions C-3 and/or C-20, which play a significant role in the compound's biochemical properties. Secondly, PPD-type saponins exhibit a linear arrangement in their glycosyl chains, further distinguishing them from other saponins. A notable example of a PPD-type saponin is ginsenoside Rb5, which features a distinctive four-glucose basic glycosyl chain with the structure Glc(2, 1)Glc(4, 1)Glc(4, 1)Glc. This particular chain is linked to the 3-OH position, contributing to the unique characteristics of ginsenoside Rb5. It is specifically isolated from the roots of *P. ginseng* and is characterized by its atypical tetra-glucosyl linear sugar chain structure, further enhancing its significance in the study of PPD-type saponins[46].

4.1.2 PPT

PPT sapogenin is characterized by its inclusion in the tetrahydroxy-substituted dammarane skeleton, which is defined by hydroxyl substitutions occurring at the C-3, C-6, C-12, and C-20 positions. This unique structural configuration is crucial for understanding the biochemical properties of the compound. A significant portion of the ginsenosides derived from this sapogenin exhibits glycosylation at the 6-OH and 20-OH positions, which enhances their solubility and biological activity. It is particularly important to highlight the classification of certain ginsenosides as Rare saponins due to their specific C-20(R) configuration.

4.1.3 OA

OA-type ginsenosides are characterized by the presence of a pentacyclic triterpenoid sapogenin called oleanolic acid. This compound typically features hydroxyl (3-OH) and carboxyl (28-COOH) functional groups that often act as sites for glycosylation, a crucial modification that influences the biological activities of these ginsenosides. In particular, research has led to the isolation of one type of OA ginsenoside from red ginseng roots, while a more diverse assortment, comprising four distinct OA-type ginsenosides, has been identified in the roots of Japanese ginseng[63, 64].

4.1.4 Other types of saponins

In addition to the three commonly recognized types of saponins, some researchers have introduced a novel classification of ginsenosides known as OT-type. This classification is distinguished by a specific structural feature: the presence of an oxygen-containing furan ring attached to the C-17 side chain, which is derived from the PPT structure. Typically, ginsenosides of the OT type possess a single glycosylation site located at the hydroxyl group on the sixth carbon (OH-6). Recently, two unique ginsenoside compounds categorized as OT type were isolated from the steamed roots of both American ginseng and Japanese ginseng, highlighting the diversity within ginsenoside structures. Moreover, the C-17 side chain of the sapogenins PPD and PPT is capable of undergoing a variety of chemical modifications. These modifications give rise to new sapogenin structures through several potential reactions, including the addition of H_2O, hydroxylation, methoxylation, and peroxidation, among others. Additional processes can include C-20 dehydration, carbonylation,

dehydrogenation, cyclization, double bond oxidation, degradation, and rearrangement, as well as combinations of these transformations. This versatility in chemical reactions illustrates the intricate nature of ginsenoside biochemistry. Beyond the subtypes previously mentioned, there exist saponins that exhibit simpler structural modifications. These modifications often involve processes such as carbonylation at specific positions, including C-3 and C-12, as well as dehydration events at C-5/C-6 or C-9/C-11. The complexity inherent in the pathways that lead to ginsenoside production, combined with the multitude of chemical reactions that can occur during processing, complicates efforts to systematically categorize these processed products into distinct saponin types. Despite originating from common saponin precursors and maintaining highly similar molecular architectures, their diverse modifications pose a significant challenge in classification.

4.2 Polysaccharides

Various types of ginseng plants are abundant in polysaccharides, showcasing considerable structural diversity. Investigations into the monosaccharide makeup of ginseng polysaccharides reveal that these substances are predominantly made up of heteropolysaccharides[65-73], with only a minimal presence of homogeneous polysaccharides. This finding underscores the intricate nature of ginseng polysaccharides, which are crucial for the biological activity in these plants. Furthermore, current studies show that the molecular weights of ginseng polysaccharides exhibit extensive variation, ranging between 3.1 and 970 kDa[65,69]. Such a wide distribution in molecular weight implies that the polysaccharides within ginseng could possess differing functional attributes and biological impacts, shaped by their size and structure. Polysaccharides may act as important resources for enhancing the understanding and exploration of the characteristics and potential application benefits of ginseng and its related products.

4.3 Peptide components (taking glycopeptide Gintonin as an example)

Alongside the previously mentioned saponins and polysaccharides, ginseng is also composed of lipids, including phospholipids, which make up roughly 1%–2% of its overall content. The amounts and types of these phospholipids in ginseng can differ based on the specific part of the plant being examined[42,74-76]. Ginseng phospholipids exhibit not only a variety in their composition, structure, and distribution but also a limited understanding of their transformations during processing. In 2011, Gintonin was successfully isolated from *P. ginseng* using anion exchange chromatography[77]. This significant discovery led to the identification of Gintonin as a novel non-saponin component distinguished by its negative charge, setting it apart from the more well-known ginsenosides found in ginseng. It was also isolated and identified in both WG and Korean red ginseng (KRG); this substance is a glycolipid protein complex with lysophosphatidic acid (LPA) as its active component. LPA is recognized as a biologically active phospholipid that influences both nervous and non-nervous systems[42,78-79]. Various animal models and clinical studies have demonstrated that gintonin possesses neuroprotective properties in both *in vitro* and *in vivo* settings[43,79-83]. Currently, the process by which gintonin LPA forms in ginseng remains unclear. It is suggested that ginseng phospholipids may significantly change during processes such as steaming and extraction/concentration, leading to the formation of ginseng Gintonin LPA, which differs from other components found in ginseng, including ginsenosides and ginseng polysaccharides.

4.3.1 *Chemical component and structure of Gintonin*

Gintonin is primarily composed of a combination of sugars, proteins, and lipids, with LPA playing a crucial role among its constituents. The composition of Gintonin reveals that it is a glycosylated protein complex, which may exist in the form of oligomers, contributing to approximately 0.2%[41] of the overall chemical makeup of *P. ginseng*. This complex exhibits a carbohydrate content of about 30%, with glucose dominating the profile at over 90%. Other sugars, such as arabinose, fructose, and galactose, are present in comparatively minor quantities[41]. The protein content is estimated to be around 30.3% and mainly includes latex-like proteins with a molecular weight of 16.8 kDa, as well as ribonuclease-like storage proteins with a molecular weight of 27.3 kDa. Notably, these proteins are rich in amino acids such as arginine, glutamic acid, and aspartic acid[41,43]. It is suggested that the proteins associated with Gintonin may serve as carriers for LPA, offering protection against hydrolytic enzymes and fostering a hydrophobic environment conducive to receptor interactions[42]. Additionally, Gintonin comprises approximately 20.2% lipids, featuring fatty acids like palmitic acid, linoleic acid, and stearic acid, along with lysophosphatidylcholine (LPC) and other analogous compounds[41]. The chemical composition of gintonin is shown in **Fig. 6**.

Gintonin and the fraction enriched in gintonin (GEF) possess considerable quantities of LPAs when contrasted with other plant medicines[42,84]. The hierarchy of LPA concentrations was found to be LPA $C_{18:2}$ >> LPA $C_{16:0}$ > LPA $C_{18:1}$ [42]. LPAs can exist in various isomeric forms based on the positioning of their acyl groups. Additionally, LPA isomers may incorporate distinct residues at the 3-phosphate head group, which can include choline, ethanolamine, glycerol, and inositol, and they can also be categorized as lysophospholipids **(Fig. 7)**. The GEF is also rich in a variety of lysophospholipids, such as LPC, lysophosphatidylethanolamine (LPE), lysophosphatidylglycerol (LPG), and lysophosphatidylinositol (LPI), although their proportions are lower compared to those of LPAs and phosphatidic acids (PAs), with their ranking in gintonin being LPC > LPE > LPG > LPI[42]. Furthermore, these lysophospholipids can be categorized as either 1-acyl-2-lyso-phospholipids or 1-lyso-2-acyl-phospholipids. The LPAs and different lysophospholipid isomers serve as ligands for GTP-binding-protein coupled receptors (GPCRs).

4.3.2 *The main active components in Gintonin*

The primary functional ligand within Gintonin, LPA, activates G protein-coupled receptors (GPCRs), specifically the LPA receptors. The LPAs and different lysophospholipid isomers serve as ligands for GPCRs. The LPAs and different lysophospholipid isomers serve as ligands for GPCRs. Up to this point, 16 GPCRs related to LPA and lysophospholipids have been identified, including one, four, and six receptors specific to LPI, lysophosphatidylserine, and LPA, respectively[85,86]. Additionally, earlier studies propose that gintonin LPI may function as a ligand for GPR55, which is recognized as an atypical cannabinoid receptor within the organism[87]. Our findings also reveal that GEF is abundant in linoleic acid compared to other free fatty acids (FFAs), and this linoleic acid from GEF may serve as a ligand for

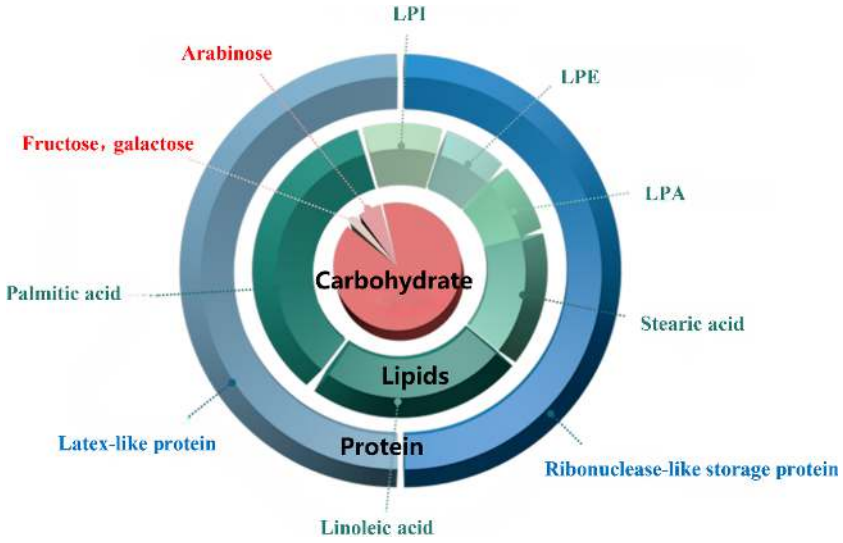

Figure 6 Schematic diagram of Gintonin substance composition.

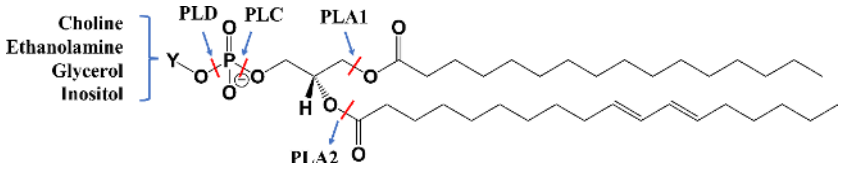

Figure 7 Schematic diagram of the composition and formation mechanism of LPAs.

GPR40, acknowledged as one of the receptors for fatty acids[88]. Therefore, ginseng comprises three exogenous ligands about the LPA receptor subtypes GPR55 and GPR40.

In addition, LPA is characterized by its structure, which includes glycerol-3-phosphate, fatty acids, and phosphates, and plays a pivotal role in stimulating increased intracellular Ca^{2+} levels. As a result of this activation, a spectrum of cellular responses may be triggered, including proliferation, differentiation, morphological changes, and cell migration. Within the composition of Gintonin, the primary bioactive components are identified as LPA $C_{18:2}$, LPA $C_{16:0}$, and LPA $C_{18:1}$, listed in descending order of their concentration[43].

4.4 Others

Research into the chemical composition of ginseng has uncovered a variety of bioactive compounds that extend well beyond the widely recognized saponins and polysaccharides. Among these discoveries is a novel fatty alkyd known as isokapsyllin, which was identified in ginseng as a result of heat treatment. The molecular structure of isokapsyllin is characterized as 14a, 15a, 16a, 17a, 18a, 19a, 20a, 21a-octahydroxy-16, 17, 18-trimethyl Base-*n*-tri-*trans*-22, 24-diene-1-acid[89]. This particular acid exhibits unique properties that may provide innovative therapeutic options warranting further research and exploration. In addition, the roots of *P. ginseng* have been found to contain four distinct polyacetylenes, which include high-alkylenic alcohols, high-alkylenic diols, (9*Z*)-heptadecan-1, 9-diene-4, 6-diyn-3-one, and (8*E*)-octadeca-1, 8-diene-4, 6-diyne-3, 10-diol[90]. These specific compounds are thought to have the ability to inhibit acetylcholinesterase, an enzyme that plays a crucial role in the breakdown of acetylcholine, a neurotransmitter essential for cognitive processes. Therefore, the presence of these polyacetylenes suggests a potential function in enhancing cognitive abilities, highlighting the importance of ginseng not only as a traditional herbal remedy but also as a candidate for further scientific study in the realm of cognitive enhancement[91].

5 Edible value of *P. ginseng*'s functional ingredients

P. ginseng has been regarded as a precious tonic by the Chinese since ancient times, with good nourishing, tranquilizing, and edifying effects. In modern research, *P. ginseng* and its concoction red ginseng have been found to be effective in the regulation of glucose and lipid metabolism, oxidative stress regulation, liver protection, and anti-fatigue, and have the potential to be developed into functional foods. These functions are attributed to the saponins, polysaccharides, oligopeptides, and other nutrients contained therein, which not only have a variety of health functions but also are non-toxic, and can be taken for a long time.

5.1 Regulation of glucose and lipid metabolism

Ginsenosides, unique compounds derived from *P. ginseng*, exhibit diverse dietary and pharmacological effects that distinguish them from one another. Among the various ginsenosides present in *P. ginseng*, Rb1 and Rg1 are the primary representatives, recognized for their widespread impact. Researchers identified and quantitatively analyzed 10 ginsenosides in red ginseng and experimentally demonstrated that red ginseng can regulate lipid metabolism and improve lipid deposition[92]. In contrast, the rare ginsenosides—such as Rg3, Rg5, and F4—are noted for their exceptional nutritional properties[93]. Research has demonstrated that the rare ginsenoside 25-OH-PPT can effectively reduce blood glucose levels and improve glucose tolerance in streptozotocin (STZ) model mice. This compound enhances insulin sensitivity by upregulating GLUT4 and AMPK in skeletal muscle, while also activating the insulin signaling pathway. Additionally, alterations in liver inflammatory factors and serum lipid profiles suggest that it possesses notable anti-inflammatory and lipid-lowering properties[94]. These findings underscore the role of rare ginsenosides and their aglycones in the regulation of glucose and lipid metabolism. It is worth noting that these rare ginsenosides

are typically found in extremely low concentrations, particularly in *P. ginseng* cultivated through artificial means. Obtaining richer amounts of rare ginsenosides requires techniques such as concoction and biotransformation.

The homology of medicine and food is not only a perspective rooted in TCM but also reflects a broader philosophy of life among the Chinese. The diverse nutritional properties of Chinese medicines can be attributed to their intricate chemical structures. These medicines consist of a wide array of molecules that form an interconnected network, and they contain substances with complex structures capable of performing multiple biological functions simultaneously. For instance, Gintonin, which has been previously discussed, exemplifies this phenomenon. The unique chemical composition and structure of Gintonin have been described in earlier studies, demonstrating its ability to induce transient changes in intracellular calcium concentration ($(Ca^{2+})_i$) through the G protein-coupled receptor signaling pathway. Furthermore, researchers have developed a straightforward method for preparing hypoglycemic agents by employing 80% ethanol extraction of ginseng root, resulting in a fraction designated as edible Gintonin[95].

5.2 Oxidative stress regulation

Ginseng polysaccharides primarily consist of neutral ginseng sugars and acidic ginseng pectin. The neutral sugars are predominantly composed of amylopectin and arabinogalactan, while the acidic pectin is characterized by a combination of rhamnose, galacturonic acid, and several other components. This composition underscores the complexity and diversity of polysaccharides in ginseng, which contribute to its various health benefits. Further analyses reveal that the water-soluble dietary fiber in ginseng is abundant in monosaccharides, including xylose and arabinose, with glucose comprising over 50% of the total monosaccharide content. This notable proportion of glucose suggests that ginseng possesses potential energy-boosting properties. Additionally, both water-soluble and insoluble dietary fibers in ginseng are rich in neutral sugars, along with a minor quantity of galacturonic acid sugars. The balance between soluble and insoluble fibers highlights ginseng's crucial role in digestive health and overall well-being. The soluble dietary fiber extracted from ginseng residue, which has a content of 8.98%, is an acidic heteropolysaccharide (with uronic acid content at 4.42%) and is rich in proteins, amino acids, and mineral elements; glucose constitutes its primary monosaccharide component (58.03%). This fiber exhibits excellent water solubility, oil retention capacity, and antioxidant activity, indicating its potential application in antioxidant foods[96].

5.3 Liver protection and anti-fatigue

Currently, there is a considerable amount of research focused on the nutritional components of *P. ginseng*, particularly ginsenosides and polysaccharides. However, there is comparatively less research on ginseng oligopeptides (GOPs), which are small-molecule oligopeptides derived from *P. ginseng*. Studies indicate that GOPs exhibit a significant protective effect against alcohol-induced liver injury, potentially mediated by the partial inhibition of the lipopolysaccharide Toll-like receptor 4-NF-κB p65 signaling pathway in the liver[97]. Furthermore, GOPs have demonstrated anti-fatigue effects, which may be attributed to their ability to inhibit oxidative stress and enhance mitochondrial function in skeletal muscle[98].

6 Multi-target pharmacology of *P. ginseng*

P. ginseng is renowned for its diverse pharmacological effects, which include anti-tumor properties, enhanced wound healing, antithrombotic capabilities, anti-inflammatory actions, regulation of the nervous system, and antidepressant effects. This impressive range of benefits has made *P. ginseng* a subject of extensive research, leading to the discovery of the synergistic interactions among its various components, which contribute to its overall pharmacological actions. Specifically, ginsenosides, which were first isolated from *P. ginseng* in the early 1960s, have been recognized as the primary active compounds responsible for many of these therapeutic effects. Traditionally, crude total ginsenoside extract (CGSF) has been favored for studying the effects of *P. ginseng*, primarily due to the difficulties associated with the purification of ginsenosides. However, recent advancements in separation technology have shed light on the limitations of using fully purified ginsenosides in isolation. Studies indicate that these purified compounds may not effectively enhance intracellular Ca^{2+} levels on their own, which implies the involvement of additional bioactive compounds present in CGSF[99-101]. Among these, Gintonin has emerged as a significant contributor, as it can swiftly elevate endogenous Ca^{2+} levels, thereby augmenting the pharmacological activity attributed to ginsenosides[78]. While both ginsenosides and Gintonin exhibit similar pharmacological effects and interact synergistically to bolster their efficacy, it is important to note that they operate via different mechanisms of action. This distinction underscores the complexity of the pharmacological properties of *P. ginseng* and highlights the potential of its various components to work in concert to produce therapeutic benefits.

6.1 Therapeutic effect on cancer

Ginsenosides are known for their anti-cancer properties, particularly through their ability to inhibit the proliferation of cancer cells. Research has revealed that one specific ginsenoside, Rg3, plays a key role in suppressing tumor growth by enhancing the expression of vaccine-related kinase 1 (VRK1) and facilitating the formation of phosphorylated specific protein (P53BP1). This process leads to the induction of DNA damage, which is detrimental to cancer cell survival[102]. Furthermore, ginsenoside Rg3 can effectively hinder cell proliferation by obstructing the NF-κB signaling pathway in human ectopic endometrial stromal cells, demonstrating that the degree of this inhibitory effect is influenced by the duration of exposure[103]. Additionally, ginsenoside Rg3 has been observed to significantly reduce cell proliferation across various human colorectal cancer cell lines, including HCT116, SW480, and HT-29, a phenomenon likely associated with the transcriptional activity of NF-κB p65 and the overall activity of NF-κB[104].

In comparison to ginsenosides, recent investigations have highlighted that Gintonin is even more effective at curbing the release of autologous toxins (ATX) and the metastasis of cancer cells. ATX is acknowledged as an autocrine factor that facilitates tumor cell movement[105], and it is often found in elevated concentrations in various cancers, including neuroblastoma, liver cancer, lung cancer, ovarian cancer, metastatic breast cancer, and melanoma; these increased levels drive the metastatic behavior of cancer cells[106]. However, there exists a strong negative feedback mechanism that serves to limit ATX activity. Studies indicate that Gintonin may function as a negative feedback regulator of ATX, demonstrating a powerful inhibitory effect on its activity[107]. In addition to this, research has shown that Gintonin can prevent the

phosphorylation of Smad2 and Smad3, which is induced by transforming growth factor-beta 1 (TGF-β1). It also decreases the expression levels of vimentin (Vim) and N-cadherin (N-cad) in the lung cancer cell line A549. Such actions contribute to maintaining the integrity of intercellular connections and effectively inhibit the metastasis of cancer cells[108].

6.2 Healing effect of wounds

Wound healing is a multifaceted process composed of several distinct yet interconnected stages, including hemostasis, inflammation, proliferation, epithelialization, and remodeling. Each of these phases plays a critical role in ensuring effective healing and recovery following tissue injury. Among these stages, the proliferation phase is particularly important as it not only involves the formation of new blood vessels through angiogenesis but also the deposition of collagen, which is essential for providing structural support to the healing tissue. The regulation of vascular endothelial cells during this phase is heavily influenced by a variety of growth factors that orchestrate their behavior and activity. Recent research has uncovered that 20(*S*)-protopanaxadiol saponins exert a significant effect on the activation of the p70S6K enzyme via two key signaling pathways: the PI3K/Akt/mTOR pathway and the Raf1/MEK/ERK pathway. This activation results in heightened expression levels of vascular endothelial growth factor (*VEGF*) mRNA as well as hypoxia-inducible factor 1-alpha (HIF-1α). Consequently, this cascade of events stimulates the proliferation of human umbilical vein endothelial cells (HUVECs)[109], thereby enhancing the process of angiogenesis which is crucial for effective wound healing. Moreover, *in vitro* experiments have illustrated that ginsenoside Rg1 serves as a potent enhancer of vascular lumen formation, and it significantly stimulates endothelial cell proliferation. This effect is achieved through its influence on the cell cycle, where ginsenoside Rg1 notably increases the population of cells transitioning into the S phase and the G2/M phase while concurrently reducing the number of cells in the G0/G1 phase. These alterations in the cell cycle promote a more robust and efficient proliferation of endothelial cells, reinforcing the importance of various bioactive compounds in the context of wound healing and tissue regeneration[110].

Gintonin has been recognized for its beneficial effects on the process of wound healing. A study conducted by Hwang *et al.*[111] illustrated that Gintonin can stimulate the activation of Rho kinase through the interaction with LPA receptors. This activation leads to significant enhancements in both the proliferation and migration of HUVECs, which are crucial components in the formation of new blood vessels during wound repair. Furthermore, Gintonin has been observed to activate cyclooxygenase-2 (COX-2) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). This activation precipitates the release of VEGF, a key player in angiogenesis, which is the process of new blood vessel formation. The ability of Gintonin to induce the release of VEGF highlights its role in fostering the necessary conditions for effective wound healing by promoting an adequate blood supply to the affected area. In addition, research by Choi *et al.*[44] uncovered that Gintonin engages phospholipase C (PLC) and inositol trisphosphate (IP3) receptors through the signaling pathway mediated by LPA1/3 receptors. This engagement results in the mobilization of calcium ions (Ca^{2+}) from mouse cortical astrocytes, which instigates the release of VEGF once again. This sequence of events reactivates the VEGF receptor/PI3K/AKT/NF-κB pathway, thereby enhancing both the proliferation and migration of keratinocytes, the primary cells involved in the wound healing process. Moreover, Gintonin also promotes the release of hyaluronic acid and collagen from human skin fibroblasts via its action on LPA receptors (**Fig. 8**). Fibroblasts are instrumental in the proliferation and remodeling stages of wound healing, thus their stimulation by Gintonin further underscores its capacity to accelerate skin wound healing. Collectively, the various signaling pathways activated by Gintonin work synergistically to enhance and facilitate the complex processes involved in the healing of skin wounds[112, 113].

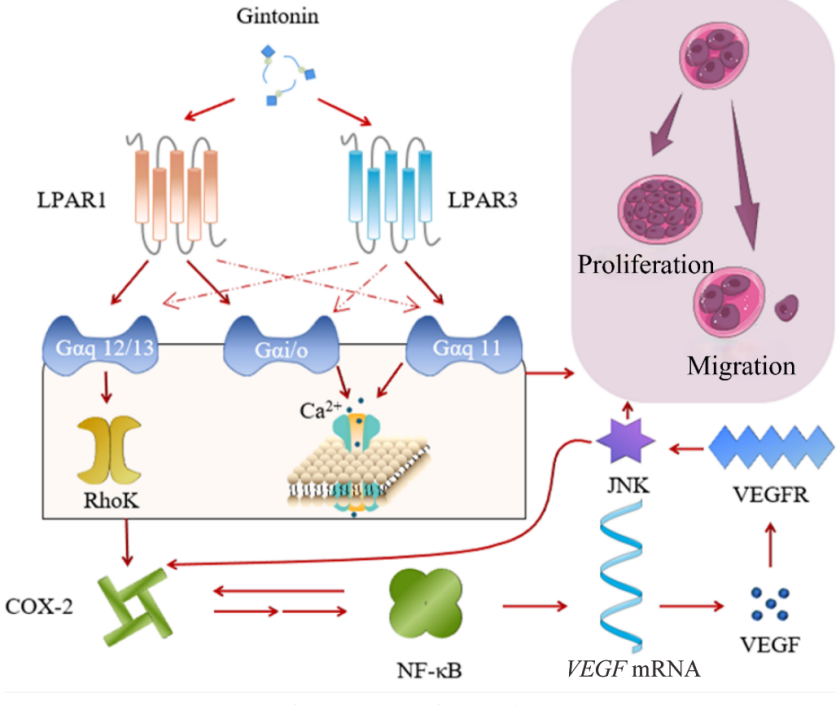

Figure 8 Schematic diagram of the mechanism of Gintonin's angiogenesis and wound healing.

6.3 Antithrombotic effect

Following a vascular injury, the process of platelet activation and aggregation can lead to the formation of blood clots, which play a significant role in the development of cardiovascular diseases. This process is critical as the accumulation of platelets can obstruct blood flow, potentially resulting in severe health complications. Research has demonstrated that ginsenosides, which are active compounds derived from ginseng, possess properties that can effectively prevent the formation of thrombi, or blood clots. They achieve this by facilitating the phosphorylation of vasodilator-stimulated phosphoprotein (VASP), while simultaneously inhibiting the phosphorylation of key signaling molecules such as phosphatidylinositol 3-kinase (PI3K) and protein kinase B (Akt). This dual action contributes to a decrease in the adherence of adhesion proteins, like fibrinogen and fibronectin, to the integrin αIIb/β3 on the surface of platelets, which is essential for proper platelet aggregation and clot formation[114]. For example, ginsenoside Ro has been found to promote the phosphorylation of VASP through the action of cyclic adenosine monophosphate (cAMP), which acts as a second messenger in various cellular signaling pathways. This mechanism results in the effective inhibition of fibrinogen binding to the integrin αIIb/β3 receptor, thereby suppressing thrombin-induced platelet aggregation. Consequently, the antithrombotic properties of ginsenoside Ro become evident, showcasing its potential to mitigate the risks associated with excessive blood clot formation and cardiovascular disease progression. Through such mechanisms, ginsenosides may offer a beneficial strategy for preventing thrombus-related complications[115].

Platelet glycoprotein I (GPVI) is recognized as a significant target in the development of antithrombotic therapies. When GPVI is activated, it sets off a cascade of downstream signaling pathways that enhance the formation of fibrin, which is a crucial component in the clotting process. This activation facilitates the binding of fibrinogen to integrin αIIb/β3 on the surface of platelets, ultimately leading to platelet aggregation and the formation of a thrombus, or blood clot. Gintonin exhibits noteworthy antithrombotic effects by specifically inhibiting the activation of GPVI. By doing so, it effectively suppresses the activity of key downstream molecules such as Src family kinases (SFK), tyrosine kinase (Syk), and PLC γ-2. Furthermore, Gintonin also demonstrates the ability to inhibit the phosphorylation of the PI3K/Akt pathway and mitogen-activated protein kinase (MAPK) signaling pathways. Notably, it inhibits the phosphorylation of mitogen-activated protein kinase 4 (MKK4), which acts as an upstream activator of c-Jun N-terminal kinase (JNK) in the MAPK pathway. This multifaceted inhibition contributes to the prevention of thrombosis in mice, highlighting Gintonin's potential as a therapeutic agent[110]. In summary, Gintonin impedes thrombosis through various pathways and targets, showcasing its complex mode of action. Although the mechanisms by which Gintonin exerts its antithrombotic effects differ from those of ginsenosides, it is important to note that these compounds can work in a complementary manner. Together, they may regulate and enhance each other's effects, leading to a more comprehensive and effective approach to managing thrombotic disorders.

6.4 Inflammatory suppressive effect

The NF-κB and MAPK signaling pathways play integral roles in the onset and progression of inflammation within the body. These pathways are critical mediators that, when activated, can lead to heightened inflammatory responses. Interestingly, both ginsenosides and Gintonin have been identified as compounds with significant anti-inflammatory properties, primarily through their ability to inhibit these signaling pathways. Research indicates that specific ginsenosides, such as Rb2 and Rg1, effectively suppress the AMPK/NF-κB signaling pathway. This inhibition is noteworthy as it contributes to a reduction in inflammatory markers, ultimately leading to a lessening of inflammation[116-118]. In contrast, Gintonin exhibits its anti-inflammatory effects by targeting both the MAPK and NF-κB pathways. It achieves this by downregulating the expression of transforming growth factor kinase 1 (TAK-1) while also enhancing the expression of certain anti-inflammatory microRNAs, namely miR-34a and miR-93[119]. Moreover, Gintonin's ability to counteract inflammation is further exemplified through its suppression of several pro-inflammatory cytokines. It inhibits the expression of key inflammatory mediators such as COX-2, inducible nitric oxide synthase (iNOS), and tumor necrosis factor-alpha (TNF-α). This is accomplished by interfering with the activity of AP-1 transcription factors, which are pivotal in promoting inflammatory responses[120]. Consequently, Gintonin plays a significant role in mitigating inflammation, highlighting its potential therapeutic use in managing inflammatory conditions.

6.5 Effects on the nervous system

6.5.1 Therapeutic effect on Huntington's disease

Huntington's disease (HD) is a neurodegenerative disorder that progresses over time and is linked to genetic factors. The underlying mechanism involves an abnormal increase in the number of glutamine trinucleotide repeats, which results in harmful aggregation of neuronal cells[121]. This aggregation contributes to several deleterious processes, including mitochondrial dysfunction and deceleration of energy metabolism in the striatum, a critical region of the brain affected by the disease. Recent studies have suggested that ginsenosides, which are compounds derived from ginseng, have the potential to alleviate striatal toxicity. They do so by inhibiting the activation of critical signaling pathways, specifically the MAPK and NF-κB, which play significant roles in neuroinflammation and neuronal degeneration. By targeting these pathways, ginsenosides exhibit neuroprotective effects that may benefit individuals suffering from HD[122]. Moreover, both Gintonin and ginsenosides are reported to operate through similar mechanisms that help mitigate the adverse effects associated with HD, including promoting the recovery of damaged nerves and reducing striatal toxicity. Gintonin, specifically, has been found to enhance the expression levels of PLCβ-3 and 1, 4, 5-triphosphate inositol receptor (IP3R) via activation of LPA receptors. This upregulation facilitates the separation of the Keap1-Nrf2 complex, which is crucial for cellular defense against oxidative stress. Consequently, Gintonin aids in protecting neuronal cells from the striatal toxicity that can be triggered by substances such as 3-nitropropionic acid (3-NPA). This protective mechanism emphasizes the potential of Gintonin as a therapeutic option for managing the challenges presented by HD[123].

6.5.2 Therapeutic effect on Alzheimer's disease

Alzheimer's disease (AD) is characterized by the aggregation and precipitation of beta-amyloid protein (Aβ) to form senile

plaques and dysfunction of the cholinergic system in the brain[124]. Over time, the accumulation of Aβ leads to neuronal cell death, brain atrophy, structural abnormalities, and cognitive impairment[125]. Gintonin and ginsenosides have been shown to alleviate AD through various mechanisms including inhibiting Aβ formation, reducing oxidative stress damage, and enhancing the cholinergic system. Ginsenosides work by inhibiting *β*- and *γ*-secretase activity, reducing acetylcholinesterase activity, and decreasing reactive oxygen species induced by Aβ[126]. On the other hand, Gintonin components improve learning and memory deficits by enhancing the cholinergic system in the hippocampus and promoting the formation of non-amyloid proteins. Additionally, they stimulate the release of soluble amyloid beta precursor alpha (sAβPPα), which helps in restoring brain function damaged by AD[125].

6.5.3 *Therapeutic effects of Parkinson's disease*

Parkinson's disease (PD) is a neurodegenerative disorder that is marked by the aggregation and deposition of Aβ, leading to the formation of senile plaques[127, 128]. This pathological process is further complicated by a dysfunction in the cholinergic system within the brain. As the levels of Aβ progressively increase, they contribute to neuronal cell death, causing brain atrophy and structural abnormalities. Ultimately, these changes are detrimental to cognitive function, resulting in significant impairments in memory and other cognitive abilities. Recent research indicates that both Gintonin and ginsenosides can play a crucial role in alleviating the symptoms associated with PD through a variety of mechanisms. One of the primary actions of ginsenosides involves the inhibition of *β*-secretase and *γ*-secretase activities, which are essential for Aβ formation. Moreover, ginsenosides are effective at reducing the activity of acetylcholinesterase, an enzyme that breaks down acetylcholine, thereby preserving levels of this neurotransmitter. Additionally, they help mitigate oxidative stress by decreasing the production of reactive oxygen species that are induced by Aβ, which collectively contributes to neuronal protection. Gintonin, on the other hand, has been shown to enhance learning and memory, particularly for deficits observed in individuals with AD. Its components work by improving the functionality of the cholinergic system located in the hippocampus, a critical area of the brain associated with memory and learning processes. Furthermore, Gintonin promotes the synthesis of non-amyloid proteins, which contribute positively to cognitive health. In addition to these benefits, Gintonin stimulates the release of sAβPPα, a protein that has been associated with neuroprotective effects, ultimately aiding in the restoration of brain function impaired by PD[129].

6.5.4 *Therapeutic effect on depression*

Depression stands as the most common mental health disorder worldwide, characterized by a multifaceted etiology that involves an interplay of various factors, including immune system irregularities and imbalances in gut microbiota. Numerous studies have highlighted that individuals suffering from depression possess elevated concentrations of inflammatory markers in their bodies, notably TNF-α and interleukin-6 (IL-6)[130]. These findings suggest a significant link between inflammation and the pathophysiology of depression, emphasizing the importance of understanding these biological mechanisms. *P. ginseng*, a well-known TCM recognized for its antidepressant effects, contains bioactive compounds such as ginsenoside Rf. Research has demonstrated that ginsenoside Rf can significantly lower the levels of inflammatory markers in the ganglia of rats and improve depressive behaviors associated with neuropathic pain. These findings indicate that *P. ginseng* may offer a therapeutic avenue for addressing inflammation-related depressive symptoms[131]. Moreover, ginsenoside Rg1, another constituent of *P. ginseng*, has been found to reduce oxidative stress and mitigate neuroinflammation. This is believed to occur through the modulation of the NOX1/NOX4 pathway, which provides a mechanism by ginsenoside Rg1 promotes neuronal health and resilience against stressors that can exacerbate depressive states. Additionally, gintonin, another significant component of *P. ginseng*, influences cellular calcium dynamics in neuroendocrine tumor cells (BON) by activating LPA receptors. This activation not only elevates intracellular calcium concentrations but also triggers the release of serotonin (5-HT), a neurotransmitter closely associated with mood regulation. Gintonin's ability to stimulate serotonin release further supports the potential of *P. ginseng* derivatives in alleviating depressive symptoms in experimental models, such as mice. Through these multifaceted mechanisms, *P. ginseng* and its components present promising prospects for depression treatment, particularly in the context of inflammation and neurotransmitter regulation[132].

7 Processing technology of *P. ginseng*

Rare ginsenosides exhibit significant biological activity that holds promise for various applications. Nevertheless, the concentration of these beneficial compounds found in raw materials sourced from *P. ginseng* tends to be relatively low. To address this limitation and bolster the production of rare ginsenosides, researchers and practitioners have employed a range of techniques. These methods encompass processing techniques, microbial fermentation, and biotransformation strategies, all aimed at increasing the yield of these valuable compounds.

7.1 Physical and chemical processing

7.1.1 *Methods*

Section 2.2 provides a comprehensive overview of the historical development of ginseng processing. In contemporary practices, the majority of ginseng production facilities and locations in China continue to utilize the time-honored steaming method as their primary technique. As delineated in **Table 5**[133-142], the regulations guiding ginseng processing are meticulously documented in the "*Chinese Pharmacopoeia*" from 1963 to 2020. Despite the influence of modern scientific and technological advancements on ginseng processing methods, there remains a strong commitment to maintaining traditional practices. Essential techniques in the processing of ginseng include purification, cutting, grinding, pounding, raw sun-drying, and steaming, which collectively produce a variety of marketable ginseng products such as ginseng powder, ginseng slices, raw sun-dried ginseng, red ginseng, and sugar ginseng. In recent years, a new variant of ginseng, known as black ginseng, has emerged within the field of ginseng processing. However, it is important to note that, at this time, there are no formally established processing specifications or standards specifically for black ginseng. The innovative processing technology for black ginseng typically involves a combination of steaming and fermentation processes. The application of repeated steaming and drying cycles initiates the Maillard reaction, which is responsible for the resulting browning of the product. This reaction also causes significant changes in the levels of reducing

Table 5 Overview of processing methods of red ginseng in the previous edition of Chinese Pharmacopoeia

No.	Edition	Processing method	Reference
1	1963	Remove the reed, cut it into sections moisten it thoroughly, and slice it	[133]
2	1977	Remove the reed, cut it into sections or moisten it thoroughly, slice and dry it, or crush it when needed	[134]
3	1985	Remove the reed, moisten it thoroughly, slice it thinly, dry it, or crush it when needed	[135]
4	1990	Remove the reed, moisten it thoroughly, slice it thinly, dry it, or crush it when needed	[136]
5	1995	Moisturize thoroughly, slice thinly, dry, or crush when used	[137]
6	2000	Moisturize thoroughly, slice thinly, dry, or crush when used	[138]
7	2005	Moisturize, slice thinly, dry, crush, or crush when needed	[139]
8	2010	Moisturize, slice thinly, dry, crush, or crush when needed	[140]
9	2015	Moisturize, slice thinly, dry, crush, or crush when needed	[141]
10	2020	Moisturize, slice thinly, dry, crush, or crush when needed	[142]

sugars, amino nitrogen, and melanoidins, which, in turn, contributes to a gradual transition in color from yellow-white to reddish-brown, and ultimately to purple-black. The concept of black ginseng was initially introduced in Korea, where the processing method entails exposing ginseng, the base medicinal ingredient, to approximately nine cycles of steaming and drying to achieve its distinct characteristics. But no matter how the processing methods and techniques evolve, their mechanisms are interconnected[143].

7.1.2 *Mechanism*

The root and rhizome of *P. ginseng*, commonly referred to as WG, serve as a foundation for various product forms, including red ginseng, which undergoes two or three cycles of steaming, and black ginseng, which experiences nine cycles of steaming. Additionally, there are numerous types of fermented ginseng products. The chemical changes that occur during the processing of ginseng are intricate and encompass a holistic perspective. The use of high-performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC-MS) methods has proven to be effective in analyzing the alterations in the content of ginsenosides and carbohydrates. These techniques provide valuable insights into the transformation networks that are stimulated by the processing of ginseng. Steaming is a widely employed method for processing raw ginseng due to the relative simplicity of the necessary preparation conditions. The mechanisms that drive these transformations are complex and can include various processes such as hydration, dehydration, hydrolysis of glycosyl groups, acetyl groups, and malonyl groups, as well as cycloaddition and isomerization. Following the steaming process, malonyl ginsenosides become susceptible to hydrolysis through mechanisms like demalonylation (removal of $-C_3H_2O_3$) or decarboxylation (removal of $-CO_2$). This hydrolysis results in the production of neutral ginsenosides, such as Rb1, Rb2, Rb3, and Rc, along with the acetyl ginsenoside 20(S)-Rs3. Furthermore, 20(S)-Rs3 can be synthesized from Rs1 or Rs2 by sequentially eliminating Glc and Ara, which may be in either pyranose or furanose forms, that are attached at C-20. Additionally, 20(S)-Rs3 can undergo further dehydration processes to create Rs4 and Rs5[144]. Interestingly, Rs4 and Rs5 might engage in additional reactions, potentially regenerating 20(S)-Rs3 as well as forming 20(R)-Rs3[145]. The conversion of ginsenosides Rb1, Rb2, Rb3, and Rc into Rd is facilitated by the loss of their terminal sugar units at C-20. Following a process known as deglycosylation, occurring at either C-3 or C-20, Rd can be transformed into F2 and 20(S/R)-Rg3[146]. The transitions between 20(S/R)-Rg3 and Rg5/Rk1 are feasible and can be achieved via dehydration reactions. Furthermore, Rg3 has the potential to lose its terminal glycosyl group at C-3, leading to the formation of Rh2[147].

The dehydration that occurs at C-20 of Rh2, along with the elimination of the terminal glycosyl moiety at C-3 of Rk1, can lead to the formation of compounds Rh3 and Rk2, respectively. This transformation indicates a specific metabolic pathway where polar PPD-type ginsenosides transition through dehydrative processes. Notably, the conversion from Rg3 to Rk1 or Rg5, as well as from Rh2 to Rk2 or Rh3, occurs preferentially through the loss of water rather than through complete degradation to the PPD sapogenin during the steaming process of *P. ginseng*. This suggests that certain structural elements are retained even under conditions that traditionally lead to more extensive degradation. Moreover, the removal of the sugar chain at C-20 from Rb1 results in the production of 20(S/R)-Rg3. This compound can further transform, leading to the formation of (20S, 25)-epoxy-Rg3 and (20R, 25)-epoxy-Rg3 through cycloaddition at C-20. Additionally, 20(S/R)-Rg3 can participate in hydration or dehydration reactions at C-20, yielding 20(S/R)-25-OH-Rg3 and compounds like Rg5 or Rk1. The subsequent transformation of 20(S/R)-25-OH-Rg3 and Rg5/Rk1 into 25-OH-G-Rg5 and 25-OH-G-Rk1 indicates a complex interplay of hydration and dehydration processes that modify these ginsenosides. Similar to the aforementioned PPD-type transformations, analogous mechanisms are observed among the PPT-type ginsenosides. For instance, hydration reactions at C-24 and C-25 of 20(S/R)-Rg2 lead to the creation of 20(S/R)-Rf2[148]. The processes of deadenylation and deacetylation of compounds like m-Re and Ac-Re both yield Re, which shows a propensity to eliminate sugar units at C-6 or C-20, forming Rg1[144, 149]. Notably, Re can lose the glucosyl residue at C-20 and subsequently undergo dehydration, resulting in the generation of 20(S/R)-Rg2 and Rg6/F4[144, 150]. Additionally, Rh4/Rk3 and 20(S)-Rf2 can be generated through either the elimination of the terminal glycosyl group at C-6 of F4/Rg6 or hydration reactions at C-20 of 20(S/R)-Rg2[151]. Rh1 can be obtained by removing the sugar residue from either C-20 of Rg1 or C-6 of Rf and Rg2[148, 152] and it can further be converted into Rh4/Rk3 via hydration. Likewise, Rg6/F4 and Rh1 may undergo additional reactions, leading to the formation of 20(S/R)-Rg2 and Rh4/Rk3[145, 152]. Lastly, Rf can originate from 20-*O*-glu-Rf and may experience dehydration at C-20, resulting in the formation of Rg8 or Rg9[144]. This illustrates the intricate metabolic pathways associated with ginsenosides, revealing their complex chemical interactions and transformations. The representative reactions of saponin components during the steaming process of ginseng are shown in **Fig. 9**.

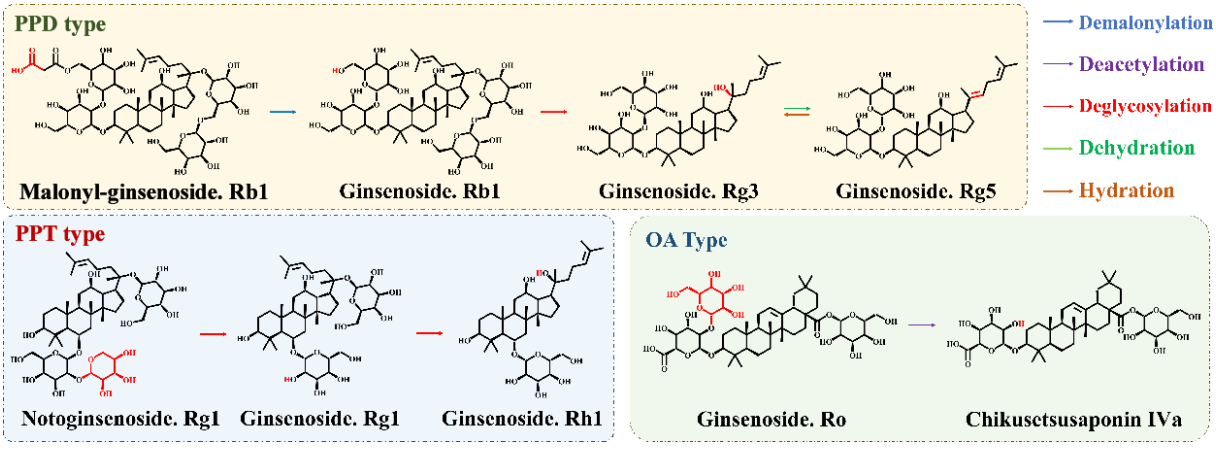

Figure 9 Schematic diagram of transformation of ginsenosides during processing.

7.2 Fermentation engineering and biotransformation

7.2.1 Methods

Various types of bacteria and fungi have shown potential in the cultivation of rare ginsenosides. Among these, ginsenoside Rb1 is particularly noteworthy as it can act as a substrate in the biosynthesis of other valuable ginsenosides, specifically Rd and Rh2 when exposed to the effects of the fungus *Aspergillus niger* 123 or various bacterial species. This bioconversion highlights the significant role that microorganisms can play in the efficient production of bioactive compounds from natural sources. Enzymes are crucial players in the complex process of saponin synthesis. They facilitate essential reactions, allowing glycosides or partial saponins to undergo glycosylation, where additional sugar units are appended, a process made possible through enzymatic action. This enzymatic intervention not only enables the modification and enhancement of the chemical structure of saponins but also plays a vital role in the hydrolysis of these compounds. For example, the enzyme MJM60396 is capable of hydrolyzing Rb1, yielding a range of bioactive saponins, including Rg3, and Rh2[153], thus illustrating the diverse enzymatic pathways that can be exploited to enhance the production of valuable ginsenosides.

7.2.2 Mechanism

In the context of ginseng biosynthesis, ginsenosides stand out as the primary focus of research and interest. Ginseng is known to contain a diverse array of saponins, which are glycosides derived from a structure known as sapogenins. These saponins can be categorized into two main types based on their chemical structure: triterpenoid saponins and steroidal saponins. Notably, ginsenosides fall into the category of triterpenoid saponins, highlighting their significance in ginseng research. The biosynthesis of saponins, including ginsenosides, generally follows a recognized pathway that can be outlined in three distinct stages. The initial phase of this process involves two critical pathways that contribute to the production of synthetic precursors[154,155]: the mevalonic acid (MVA) pathway[156-158] and the 2-C-methyl-*D*-erythritol 4-phosphate (MEP) pathway[159,160]. These pathways are essential for generating the necessary compounds that will ultimately lead to the synthesis of various types of saponins, including the bioactive ginsenosides. Through understanding these pathways, researchers can gain insights into the mechanisms underlying the production of these important compounds in ginseng.

8 Products

Ginseng products are derived from ginseng herbs through specific processes tailored to market demands, and they can serve both medicinal purposes and consumption with added value. These products encompass a range of items, including ginseng Decoction piece, proprietary Chinese medicines containing ginseng, ginseng health foods, functional foods with ginseng, ginseng cosmetics, and daily chemical products infused with ginseng.

8.1 Processed products

Decoction piece is a distinctive pharmaceutical form of TCM, derived from herbs through a process of processing. Currently, they are the predominant form of medication utilized in TCM clinics. The expansion of ginseng decoction pieces has significantly broadened the applications of ginseng. Beyond red ginseng, a growing variety of products have emerged on the market, including sun-cured ginseng, boiled ginseng, sugar ginseng, active ginseng, and black ginseng. Additionally, several new types of ginseng decoction pieces are presently available, including[161] 1) freeze-dried ginseng slices, which are produced by cutting fresh ginseng after purification and subjecting it to vacuum freeze-drying; 2) red ginseng slices, derived from red ginseng during the cutting process; 3) ultra-thin ginseng slices, obtained by cutting fresh ginseng followed by low-temperature drying and sterilization; and 4) ginseng dispensing granules, which are created from single ginseng decoction pieces through a specialized process for direct consumption. In recent years, the Chinese government has actively encouraged and guided Herbal medicine production enterprises to source freshly cut ginseng products from local provinces, aiming to maximize the retention of active substances and enhance the quality of the decoction piece.

8.2 Food products

The raw materials for the development of ginseng health foods are not limited to the rhizome of *P. ginseng*, traditionally recognized as a medicinal herb; rather, all parts of the *P. ginseng* plant have been fully utilized. Ginseng leaves and fruits are now included in the list of substances approved for use in health foods. In December 2023, China's health department formally released the 'Health Food Raw Material Catalog of *P. ginseng*' along with supporting documents, officially incorporating ginseng into the catalog of raw materials for health food registration[162]. The primary benefits of ginseng health foods are their ability to

enhance immunity and reduce fatigue. Consequently, many commonly used Chinese medicinal herbs in these formulations are tonic herbs, such as wolfberry, astragalus, epimedium, and deer antler. The combination of *P. ginseng* with these herbs has proven to be particularly effective in boosting immunity and alleviating fatigue.

In addition to its role as a health food, *P. ginseng* is incorporated into traditional Chinese diets, often featured in beverages such as tea and in various stews. In 2012, *P. ginseng* received approval as a new resource food (NRF), marking its entry into the modern food industry. Currently, ginseng is available in various product forms, including tea, wine, candies, royal jelly, honey tablets, syrups, cookies, and bread[163]. Recently, a diverse array of ginseng beverage products has emerged, including ginseng coffee, ginseng polysaccharide fermented milk drinks, ginseng milk drinks, ginseng goji berry yogurt, ginseng eight treasures tea, and ginseng cola.

8.3 Cosmetics

Ginseng extracts and saponins have been extensively studied in the context of skincare, demonstrating significant effects such as anti-aging, skin whitening, and wrinkle reduction[164]. Various parts of the ginseng plant, including roots, stems, leaves, flowers, fruits, and seed oils, contain active compounds known as ginsenosides, which possess notable cosmetic and skin-care properties. Furthermore, these parts of ginseng, along with their extracts, ferments, and tissue cultures, have received approval from the State Food and Drug Administration (CFDA) for use as raw materials in cosmetic products.

8.4 Personal care products

The hydroxyl group contained in ginsenosides can generate hydrogen bonds with hydrophilic groups, which increases the absorption of saponins into the hair and thus has a hair care effect, and the vitamins and trace elements contained in ginseng also have a similar effect[164]. Currently, the types of ginseng products on the market are mainly shampoos and body washes, and their effects are mostly cleansing and nourishing.

9 Summary and outlook

P. ginseng has been utilized as a fundamental raw material in traditional medicine and culinary practices in China for centuries. Over the years, the evolution of modern analytical and pharmacological methodologies has allowed researchers to achieve an in-depth understanding of *P. ginseng*'s complex composition and its associated biological activities. These advancements have contributed significantly to the knowledge surrounding this esteemed herbal remedy. Despite these substantial strides, the contemporary development and application of *P. ginseng* in the field of nutrition have not kept pace. The exploration of *P. ginseng*'s nutritional components, alongside a comprehensive investigation into their underlying mechanisms, remains significantly underdeveloped. Based on the analysis above, it is believed that the future challenges facing *P. ginseng* research and product development primarily involve the following aspects: 1) Nutritional and food science research must clarify the nutritional and functional ingredients, as well as their mechanisms; 2) The boundaries between functional foods and drugs require further clarification regarding their material basis, usage, and dosage; 3) Product manufacturing needs to transition from traditional processing techniques to methods that align with modern food technology or pharmaceutical engineering. This oversight presents a valuable opportunity for further research and exploration, suggesting that delving deeper into these aspects of *P. ginseng* could yield important insights and benefits in nutritional science. Therefore, advancing the study of *P. ginseng*'s nutritional properties and their effects is an essential direction for future inquiry.

Conflicts of interest

Liang Feng is an associate editor of the journal, but was not involved in the processing, peer review or decision making of this article.

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