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Review

Phytochemistry, quality control and biosynthesis in ginseng research from 2021 to 2023: A state-of-the-art review concerning advances and challenges

Mengxiang Ding [1], Huizhen Cheng [1], Xiaohang Li [1], Xue Li, Min Zhang, Dianxin Cui, Yijin Yang, Xiaojin Tian, Hongda Wang *, Wenzhi Yang *

State Key Laboratory of Chinese Medicine Modernization, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China
Haihe Laboratory of Modern Chinese Medicine, Tianjin 301617, China

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ABSTRACT

Panax L. (Araliaceae) has a long history of medicinal and edible use due to its significant tonifying effects, and ginseng research has been a hot topic in natural products research and food science. In continuation of our recent ginseng review, we highlighted the advances in ginseng research from 2021 to 2023 with 157 citations, which exhibited the increasingly systematic, collaborative, and intelligent characteristics. In this review, we firstly updated the progress in phytochemistry involving the ginsenosides and polysaccharides and summarized the researches on the active components. Then, some specific applications by feat of the multidimensional chromatography, mass spectrometry imaging, DNA barcoding, and metabolomics, were analyzed, which could provide rich information supporting the multi-component characterization, authentication, and quality control of ginseng and the versatile products. Finally, the recent biosynthesis studies concerning ginsenosides were retrospected. Additionally, the current challenges and future trends with respect to ginseng research were discussed.

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* Corresponding authors.
E-mail addresses: hdwang_1996@163.com (H. Wang), wzyang0504@tjutcm.edu.cn (W. Yang).
[1] These authors contributed equally to this work.

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1. Introduction

Medicinal herbs have been utilized for a long period to prevent and treat the disease in numerous cultures around the world. The US Food and Drug Administration (FDA) has approved an increasing number of plant-based natural products or their derivatives as the new drugs (Newman & Cragg, 2020). *Panax* plants of the Araliaceae family are the precious medicinal herbs, such as *Panax ginseng* C. A. Meyer (PG), *Panax quinquefolius* L. (PQ), *Panax notoginseng* (Burk.) F. H. Chen (PN), *Panax japonicus* C. A. Meyer var. *major* (Burk.) C. Y. Wu et K. M. Feng (PJm), *Panax japonicus* C. A. Meyer (PJ), *Panax stipuleanatus* C. T. Tsai & K. M. Feng (PS), etc., which play important roles in compatibility of different prescriptions. *Panax* species are widely distributed in the East Asia and North America (Editorial Committee of the Flora of China of Chinese Academy of Science, 1993). Especially, the ginseng products are available in various forms, including the extracts, processed products, nutritional health products, dietary upplements, and energy drinks (Yue, Zuo, Huang, & Wang, 2021). The economic value of ginseng in the global trade of medicinal plants is expected to reach $17.7 billion by 2030 (Fang, Tang, Wei, Feng, & Yu, 2023).

Ginsenosides, naturally occurring as the oligo-glycosides of tetracyclic triterpenes or pentacyclic triterpenes, are the primary active components of ginseng, which are the material basis for treating various diseases and chemical markers for quality control. The known ginsenoside compounds, in structure, mainly involve four subclasses, such as the protopanaxadiol type (PPD), protopanaxatriol type (PPT), oleanolic acid type (OA), and octillol type (OT). It was found that the ginsenosides in PG, PQ, and PN, were primarily the tetracyclic triterpenes (Li, et al., 2022c), such as ginsenosides Rg_1, -Re, -Rb_1, -Rd, etc., whereas the ginsenosides in PJm, PJ, and PS, were mainly the pentacyclic triterpenes (Liu et al., 2022a; Shu et al., 2021; Yuan, Yin, Zhao, & Lan, 2022). For instance, PJm and PJ contained ginsenoside Ro and chikusetsusaponin IVa, while stipuleanosides R_1 and -R_2 were reported in PS. Due to their anti-cancer, anti-fatigue, and anti-aging properties, ginsenosides have shown potential clinical applications for the treatment of various diseases, including the heart disease, menopausal syndrome, tumors, diabetes, metabolic disorders, and the Alzheimer's disease (Angelova et al., 2008; Chung, Kang, & Lee, 2016; Lim, Cho, Kim, Bae, & Kim, 2014; Shi, Zeng, & Wong, 2019; Wang et al., 2023c). In addition, since the active plant polysaccharides were confirmed, there has been an unprecedented surge in the research interest on the polysaccharides in China and outside. The immunomodulatory, antitumor, antioxidant, free radical scavenging, and hypoglycemic effects of polysaccharides from *Panax* genus were comparable to those of the ginsenosides (Chen & Huang, 2019; Ferreira, Passos, Madureira, Vilanova, & Coimbra, 2015; Khan, Date, Chawda, & Patel, 2019; Wang et al., 2021b; Yoo et al., 2012). Furthermore, the *Panax* plants also contain volatile oils, flavonoids, organic acids, and other active constituents, which have antibacterial and antitumor effects.

Many analytical strategies have been developed for the qualitative and quantitative analyses of various *Panax* plants and the associated products, hence greatly promoting the quality control of ginseng. Liquid chromatography/mass spectrometry (LC-MS) provides highly sensitive, specific, and versatile structural information, which has been proven as an effective technique for the high-throughput analysis of ginsenosides, polysaccharides, and the other chemical components. LC-MS profiling combined with metabolomics was demonstrated as potent in discriminating different ginseng varieties (Li et al., 2022d; Yoon, Shin, Oh, Choi, & Young, 2022). Multi-dimensional liquid chromatography (MDLC) can significantly improve the separation performance of ginsenosides, particularly for trace ginsenosides detection (Jia et al., 2022). Rapidly developing MS scanning modes, such as data-dependent acquisition (DDA), data-independent acquisition (DIA), and the emerging hybrid scanning strategy (e.g., HDDIDDA and DDIA), are committed to enhancing the coverage, sensitivity, and reliability in acquiring the MS^2 or MS^n information (Wang et al., 2022a). In addition, the emerging mass spectrometry imaging (MSI) technology can provide the spatial distribution information of the interested compounds in the slices of various plant tissues (Li et al., 2022c). Especially, ginseng polysaccharides have highly complex advanced structures, rending a very challenging task. Studies on the structure of ginseng polysaccharides require the combination of enzymatic or chemical methods (e.g., acid hydrolysis, methylation, periodate oxidation, Smith degradation, acetylation, etc.) and physical methods [e.g., infrared spectroscopy (IR), nuclear magnetic resonance (NMR), MS, etc.] (Guo, Shao, Wang, Zhao, & Wang, 2021; Li et al., 2022c; Liu et al., 2022b). Three-level fingerprinting was established to identify the structure of ginseng polysaccharides, and more importantly, novel oligosaccharide or monosaccharide markers were primarily discovered for differentiation among six root ginseng drugs from the viewpoint of polysaccharides (Liu et al., 2022b; Liu et al., 2023). In addition,

DNA barcoding uses the recognized standard short sequence in the genome for species identification, which can distinguish and identify the confusing varieties of *Panax* herbs, as well as distinguish the feeding authenticity of formula granules or Chinese patent medicines (Xu et al., 2023c).

Using the Web of Sciences database, we globally searched the publications related to ginseng research. The keywords, including the phytochemical separation, quality control, and biotransformation, were involved in the literature searching. Performing the visual analysis by using the CiteSpace 6.3.Rl (64-bit) Basic software, the research hotspot network diagrams and keyword emergence analysis were given. After removing the irrelevant and duplicate literature, a total of 771 articles published from 2013 to 2023 were gained, 284 of which were released in 2021–2023. Analyzing the keywords of ginseng research was conducive to grasping the research hotspots and future development directions in different periods within this field. It also suggested that *Panax* research will continue to be a research hotspot in the future, involving the systematic characterization and mechanism of action. According to the analysis of research hotspots keywords (Fig. 1A), the researches mainly focused on the separation, quality control, and biotransformation of components in different *Panax* plants (particularly PG, PQ, and PN). Over the past ten years, there has been a discernible trend of transfer in the research hotspots of *Panax* plants, as indicated by the examination of keyword bursts in Fig. 1B. Notably, more attention has been drawn to the hotspots like molecular docking, network pharmacology, and the others.

Previous reviews on *Panax* mainly cover the quality control and structural identification of chemical components, pharmacokinetics, pharmacology and toxicology, pharmaceutical preparations, and the other aspects (Guo, Shao, Wang, Zhao, & Wang, 2021; Liu et al., 2022b; Mancuso & Santangelo, 2017; Piao et al., 2020; Wu et al., 2018; Zanuso et al., 2022; Zhang et al., 2020). Undoubetly, as a typical case of multi-source plants, a key segment in ginseng research is the quality control. Two high-impact reviews have been published in *Natural Product Reports* (Li et al., 2022c; Qi, Wang, & Yuan, 2011), covering the related researches to the end of 2020. As a continuity, in the current review, three aspects of ginseng research reported in the last three years (2021–2023), involving the phytochemistry (focusing on ginsenosides and polysaccharides), quality control, and biosynthetic pathways, were summarized. The current challenges encountered in ginseng analysis and future trends were also discussed.

2. Phytochemistry

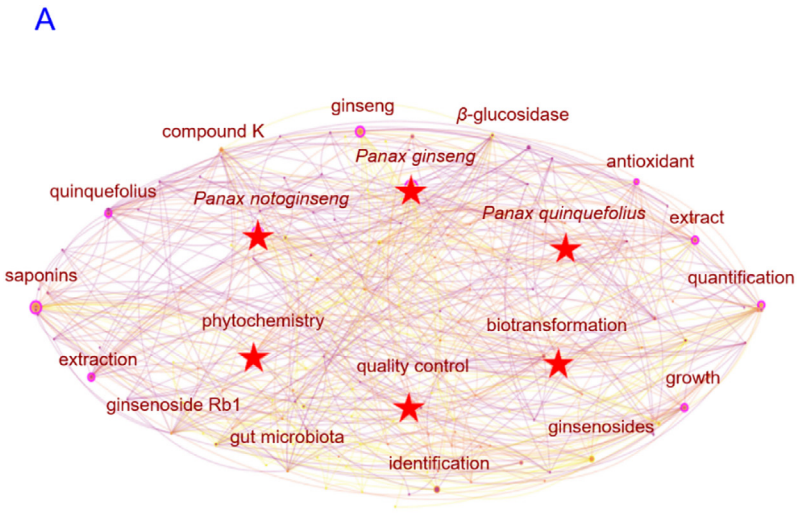
The chemical components of the *Panax* species still draw wide interest in the last three years (2021–2023) to discover new active components, including the ginsenosides, polysaccharides, peptides, essential oils, polyacetylenes, alkaloids, and alcohols, *etc.* (Shuai et al., 2023; Tran et al., 2023; Kiem et al., 2021; Wang et al., 2020). Up to now, at least 620 ginsenosides have been isolated from whole *Panax* genus, and versatile C-17 side chain varied compounds dominate the new ginsenoside structures (Li et al., 2022c). Fig. 2 shows the new ginsenosides reported in the past three years (the red circles represent the common glycosylation sites).

2.1. Ginsenosides

2.1.1. Extraction, separation, and purification

Among the common extraction methods, solvent extraction is still the most common for extracting the ginsenosides, and the polarity of the solvent has a significant impact on the solubility of ginsenosides (Cao et al., 2022; Tu et al., 2022; Yang et al., 2021). Other extraction methods include solid-phase extraction, microwave-assisted extraction, pressurized liquid extraction, enzyme-assisted extraction, accelerated solvent extraction, matrix solid-phase dispersion extraction, and pulsed electric field (Li et al., 2022c; Yang et al., 2021). Magnetic lanosterol imprinted polymers (MLIPs) were prepared using the analog of ginsenosides for the extraction of ginsenosides (Liu et al., 2021d). A new type of green solvent, deep eutectic solvent (DES), was reported (Tu et al., 2022). Compared with other commonly used solvents, it was found that the combination of choline chloride and urea in the binary DES at a ratio of 1: 2 enabled the highest extraction efficiency.

For the purification and separation of mixed components, liquid–liquid extraction, column chromatography, liquid chromatography and the other methods are often used. In recent years, the introduction of supercritical fluid chromatography (Mei et al.,



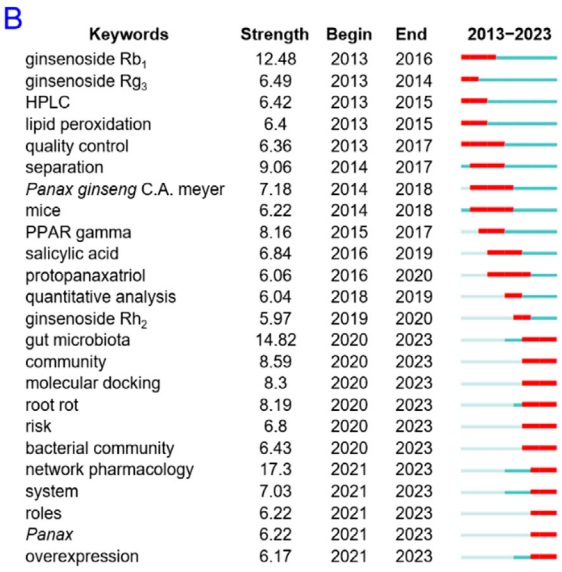


Fig. 1. Research hotspot map of ginseng research literature from 2013 to 2023. (A) Research hotspot keywords related to *Panax* plants in past three years; (B) Research hotspot changes of *Panax* plants in recent ten years (the depth of color indicates the strength, and the length indicates the start and end time).

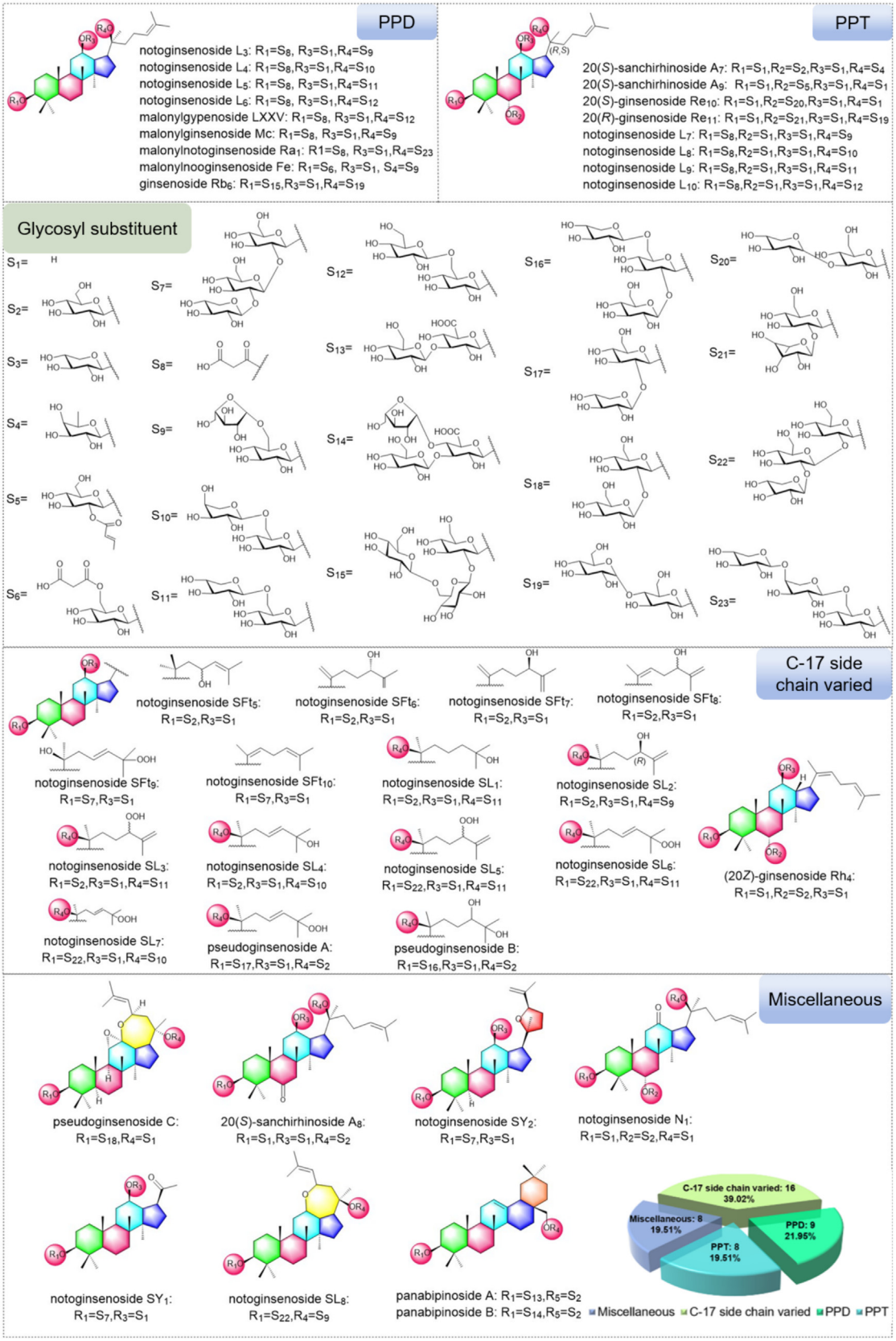


Fig. 2. Chemical structures of 41 ginsenosides from *Panax* plants.

2022), foam separation, ionic liquids, high-performance countercurrent chromatography and other methods has assisted the efficient enrichment and rapid locking of ginsenosides. In addition, the synthesis of a new stationary phase is another new and effective method for extracting the saponins. Two new stationary phases were prepared by "thiol-ene" click chemical reaction,

which outperformed the C_{18} column in separating the total saponins of *P. notoginseng* (Xie et al., 2023).

2.1.2. New compounds

New ginsenoside compounds reported in 2021−2023 were isolated from PG, PN, and *P. bipinnatifidus* Seem, and their structures were established by using the MS, infrared spectroscopy (IR), nuclear magnetic resonance (NMR), optical rotation, acid hydrolysis, and the other techniques. These analytical techniques could assist to identify the bond angle relationships, glycosyl types and configurations, as well as the coupling and connection of the C—O, C—H, C—C, and C=C bonds.

A total of 41 new ginsenosides were reported in the *Panax* genus (Fig. 2, Table S1), with the molecular masses varying between 620.428 8 ($C_{36}H_{60}O_8$) and 1 270.655 8 ($C_{60}H_{102}O_{28}$). These newly discovered ginsenosides mainly involved a varied C-17 side chain (hydroxylation, oxidation at the double bond, peroxidization, H_2O-addition, dehydration at C-20, rearrangement, or the integration of two or more of the above reactions), accounting for 39.02% of the total amount, followed by the protopanaxadiol-type (PPD-type, 21.95%), protopanaxatriol-type (PPT-type) and miscellaneous (19.51%). If viewed from the plant species, 83.33% of the newly discovered ginsenosides in the past three years originated from PN, covering its fruits, leaves, and roots.

(1) Protopanaxadiol-type (PPD, **1**−**9**)

PPD-type: The PPD-type sapogenin was characterized by the presence of three -OH groups at C-3, C-12, and C-20. Nine compounds (**1**−**9**) containing the PPD sapogenin were newly discovered between 2021 and 2023, with 88.89% of them reported from PN. Especially, in the oligosaccharide chain attached to C-20 of compound **5** (ginsenoside Rb6), the terminal Glc was substituted with the 4-OH of the inner Glc (Niu, Fan, Lv, & Lu, 2023). The remaining eight compounds were all malonyl substituted (Fig. 2), with compounds **1**−**4** being directly substituted at the 3-OH (Yao et al., 2021) and compounds **6**−**9** at various glycosyl sites (Qu et al., 2021). Notably, the fragment ions with the malonyl group characteristics can be used as an effective detection method for identifying adulteration in the PN products. In a study using the UPLC-QDa platform, a series of novel malonyl characteristic fragment ions were chosen as the quality markers to build a selective ion monitoring approach that enabled the accurate identification of PN adulteration (Yao et al., 2021).

(2) Protopanaxatriol-type (PPT, **10**−**17**)

PPT-type: Eight compounds (**10**−**17**) with the PPT-type sapogenin were newly isolated from PG and PN (Ning et al., 2023; Niu, Shi, Teng, Lv, & Lu, 2024; Yao et al., 2021). Three new dammarane-type triterpenoid ginsenosides were isolated from the roots of PN, and 20(*S*)-sanchirhinoside A7 ($C_{42}H_{72}O_{13}$) thereof was the first ginsenoside containing a fucose isolated from the *Panax* genus, which enriched the current knowledge to the glycosyl complexity of ginsenosides (Ning et al., 2023).

(3) C-17 side chain varied (**18**−**33**)

C-17 side chain varied: The subclass of C-17 side chain varied ginsenosides (**18**−**33**) exhibited structural diversity on the site of double bond, hydroxyl, carbon reduction, and the changes in the relative configuration on the C-17 chain of the PPD and PPT sapogenins. Among 16C-17 side chain varied (39.02% of the total amount), most of them (93.75%) were separated from PN. The content of the C-17 side chain varied ginsenosides in PN could increase after the steaming (Zhang et al., 2022b).

(4) Miscellaneous (**34**−**41**)

Miscellaneous: Some ginsenosides (**34**−**41**) exhibited the reactions of oxidation (Ning et al., 2023; Zheng et al., 2022), reduction (Yang, Xiong, & Shen, 2021, Kiem et al., 2021), dehydration (Hanh et al., 2022; Kiem et al., 2021), and cyclization on the cyclic parent nucleus (Hanh et al., 2022; Sun et al., 2023a), leading to the new miscellaneous ginsenosides. Eight compounds containing various sapogenins were discovered in PN and *P. bipinnatifidus*.

2.2. Polysaccharides

2.2.1. Extraction, separation, and purification

Polysaccharides are typically extracted from the *Panax* herbs using the solvents such as water, acid, alkali, and various concentrations of alcohol, assisted with the ultrasound, microwave, or enzymes (Qi et al., 2021). Crude ginseng polysaccharides can be prepared by means of alcohol precipitation (Chang et al., 2022; Guo, Shao, Wang, Zhao, & Wang, 2021; Liu et al., 2021d; Zhang et al., 2023a). By utilizing the alcohol precipitation method, the average molecular weight of the obtained polysaccharides gradually could decrease with increase of the ethanol concentration (Zhao et al., 2022).

To characterize the structure of ginseng polysaccharides, separation and purification for the removal of other components from the sample, can be a key step. For instance, the small molecular impurities can be removed by the dialysis. Lipids can be extracted using organic solvents (various concentrations of methanol, ethanol, ether or petroleum ether). The most commonly used methods for removing the pigments are the adsorption and oxidation (e.g. macroporous resin adsorption, activated carbon adsorption, and hydrogen peroxide oxidation). Several approaches are available for protein removal, such as the protease method, the Sevage method (a mixture of chloroform and *n*-butanol at a volume ratio of 4: 1), the trichloroacetic acid method (also known as the TCA precipitation method), and the trifluorotrichloroethane method (Bai et al., 2022; Nguyen et al., 2021; Ying, Ma, Zhang, Li, & Wu, 2023). In addition, ion exchange chromatography and gel chromatography are frequently utilized for purifying ginseng polysaccharides (Cao et al., 2022; Jia et al., 2021; Ying, Ma, Zhang, Li, & Wu, 2023; Zhang et al., 2023a).

2.2.2. Structural elucidation

Pure polysaccharides refer to the components giving a single symmetrical chromatographic peak determined by HPSEC or HPGPC, whose structural identification is generally performed from the following three aspects: (1) molecular weight distribution; (2) monosaccharide composition analysis; and (3) glycosidic bonds characterization. The structural analysis of ginseng polysaccharides often requires a combination of various methods (Cui et al., 2021).

Commonly used chemical methods for structural characterization of ginseng polysaccharides include the methylation, acetylation, Smith degradation, and acid hydrolysis. Congo red reagent, for example, can form a compound with polysaccharide's helical structure in alkaline solution, causing a red shift of the absorption wavelength, which can be used to confirm the existence of helical structures in polysaccharides (Lian et al., 2022; Yang, Li, Liu, Zhao, & Zeng, 2023). The phenol–sulfuric acid method is used to determine the components of carbohydrates, as one of the commonly used methods for determining the content of polysaccharides (Jia et al., 2021; Li, Liu, Yang, & Zeng, 2022). Because of the lack of UV absorption, it is common to convert the completely hydrolyzed monosaccharide components into 1-phenyl-3-methyl-5-pyrazolone (PMP) derivatives, followed by HPLC or UHPLC analysis at 250 nm. In addition, the presence of ginseng glycoprotein in

polysaccharides can be determined using the potassium iodide reaction, while the presence of amino acids or peptides can be detected using the biuret test. Protein can be identified using the double-bonded urea reagent, and the presence of monosaccharides and phenols can be determined through the reaction of iron reagent with ferric chloride (Hu et al., 2022; Wang et al., 2021b).

Some analytical methods for characterizing the structure include IR, MS, and NMR (^{1}H NMR, ^{13}C NMR), among others. The absorption peaks at 260 nm and 280 nm in the ultraviolet–visible spectrophotometer can be used to detect the presence of proteins and nucleic acids in polysaccharides (Jiang, Ma, Zhao, Meng, & Chen, 2023; Yang, Li, Liu, Zhao, & Zeng, 2023). The types of glycosidic bonds of methylated or acetylated polysaccharides can be analyzed by GC–MS (Cui et al., 2021; Jia et al., 2021). MS is able to primarily determine the accurate mass and fragments information, giving the evidence to characterize the sequence and attachment pattern of the oligosaccharides or the low polymerization degree of polysaccharides (Jia et al., 2021; Jiang, Ma, Zhao, Meng, & Chen, 2023). NMR can give reliable information regarding the types and connection modes of the glycosidic bonds (Cui et al., 2021; Li, Liu, Yang, & Zeng, 2022; Zhang et al., 2023b; Zhao et al., 2022). X-ray diffraction (XRD) can be used to analyze the crystal structure (Tao et al., 2023; Ying, Ma, Zhang, Li, & Wu, 2023), while FT-IR gives useful information with regard to the types of the functional groups, the types of glycosidic bonds, and structures of the glycosidic bonds (Jiang, Ma, Zhao, Meng, & Chen, 2023; Tao et al., 2023).

In addition, enzyme-linked immunosorbent assay (ELISA), scanning electron microscopy (SEM), and circular dichroism (CD), are frequently employed to analyze the complex high-level structures in ginseng polysaccharides (Guo, Shao, Wang, Zhao, & Wang, 2021; Qi et al., 2021; Ying, Ma, Zhang, Li, & Wu, 2023).

2.2.3. New structures

Various *Panax* plants contain a wide variety of structurally diverse polysaccharides. After processing the ginseng plants, the resulting polysaccharides are not available from the plant itself, thereby significantly increasing the structural diversity of polysaccharides. Table 1 provides the detailed information on the polysaccharides that have been isolated from the *Panax* genus in the past three years.

2.3. Others

In addition to the aforementioned ginsenosides and polysaccharides, Table 2 shows the other substances that have been discovered in ginseng plants.

3. Quality control

We researched novel analytical methods related to *Panax* medicinal materials in the past three years and discovered that they primarily focused on multidimensional chromatography, mass spectrometry scanning methods, mass spectrometry imaging, DNA barcoding, metabolomics, etc, and had been applied to multi-component characterization, content determination, and distinction and identification, among others (Fig. 3).

3.1. New analytical technology

3.1.1. Multidimensional chromatography

Multidimensional chromatography (MDC) is a separation technique which can combine the stationary phases with different mechanisms of separation, and is more suitable for characterizing the complex compound systems. It can significantly improve the separation efficiency of co-eluted ginsenosides and *iso*-differential ginsenosides in ginseng extracts. MDC can work in the online mode (Ma, Ma, Cao, & Wan, 2022; Xu et al., 2023a; Yang, Jin, Zhang, & Wang, 2023; Yang, Zhang, Zhang, Yang, & Wang, 2022) and the offline mode (Jia et al., 2022; Qu et al., 2023; Sun, Zhang, Bao, Chu, & Tong, 2022; Wang et al., 2022a).

Table 1
New polysaccharides from *Panax* species from 2021 to 2023.

Panax species	Names	Monosaccharide composition	Molecular weight	References
PG	WGFPN	Gal, Ara, Glc and Man in the ratio of 78:14.3:5.2:2.5	1.10×10^4	Cui et al., 2021
RG	RGP1-1	Glc and Gal in the ratio of 94.26:4.92	5 655	Lian et al., 2022
PG	GP1A	Glc, Gal, Man, Xyl and Ara in a molar ratio of 90.62:2.01:7.14:1.05:0.20	1.03×10^3	Ying, Ma, Zhang, Li, & Wu, 2023
PN	PNPB1	Glc, Gal, Ara and GlcA in the ratio of 88.2:9.0:2.4:0.4	9.30×10^5	Jiang, Ma, Zhao, Meng, & Chen, 2023
PN	Pan	Rha, Ara, Xyl, Man, Glc and Gal in a molar ratio of 11.7:23.3:3.27:4.7:6.4:32.6 With GlcA and GalA in a molar ratio of 2.64:4.03	8.27×10^3	Li, Liu, Yang, & Zeng, 2022
PN	Pnp	Rha, Ara, Xyl, Man, Glc and Gal in the ratio of 11.7:23.3:3.27:4.7:6.4:32.6	7.86×10^4	Yang, Li, Liu, Zhao, & Zeng, 2023

Table 2
New other types of compounds from *Panax* species from 2021 to 2023.

Compounds	Molecular formula	Resources	Types	References
Neoisomaltolide	$C_{13}H_{16}O_9$	Red ginseng	Phenol	Cho et al., 2023
(*R*,*S*)-Neofuraneolide	$C_{14}H_{22}O_9$	Red ginseng	Phenol	Cho et al., 2023
Ginsenoyne O	$C_{21}H_{30}O_5$	PG roots	Polyacetylene	Kim et al., 2022
Ginsenoyne P	$C_{21}H_{28}O_5$	PG roots	Polyacetylene	Kim et al., 2022
Ginsenoyne Q	$C_{18}H_{26}O_4$	PG roots	Polyacetylene	Kim et al., 2022
3-Acetyl panaxytriol	$C_{19}H_{28}O_4$	PG roots	Polyacetylene	Kim et al., 2022
Panaxindole	$C_{18}H_{23}NO_8$	*P. vietnamensis* leaf	Indole alkaloid	Vu et al., 2023
Jasmogin A	$C_{12}H_{20}O_4$	Wild PG adventitious root	Cur-cubinoyl derivative	Liu et al., 2021c
Jasmoflagin A	$C_{33}H_{40}O_{13}$	Wild PG adventitious root	Curcubinoyl-conjugated flavanone derivative	Liu et al., 2021c
Jasmoflagin B	$C_{33}H_{40}NaO_{13}$	Wild PG adventitious root	Curcubinoyl-conjugated flavanone derivative	Liu et al., 2021c
Jasmoflagin C	$C_{33}H_{38}O_{13}$	Wild PG adventitious root	Curcubinoyl-conjugated flavanone derivative	Liu et al., 2021c
Jasmoflagin D	$C_{33}H_{40}NaO_{12}$	Wild PG adventitious root	Curcubinoyl-conjugated flavanone derivative	Liu et al., 2021c
Jasmoflagin E	$C_{33}H_{40}O_{13}$	Wild PG adventitious root	Curcubinoyl-conjugated flavanone derivative	Liu et al., 2021c
Jasmoflagin F	$C_{33}H_{43}NO_{13}$	Wild PG adventitious root	Curcubinoyl-conjugated flavanone derivative	Liu et al., 2021c
Panaxolide	$C_{15}H_{22}O_4$	*P. vietnamensis* leaf	Sesquiterpene lactone	Le et al., 2022

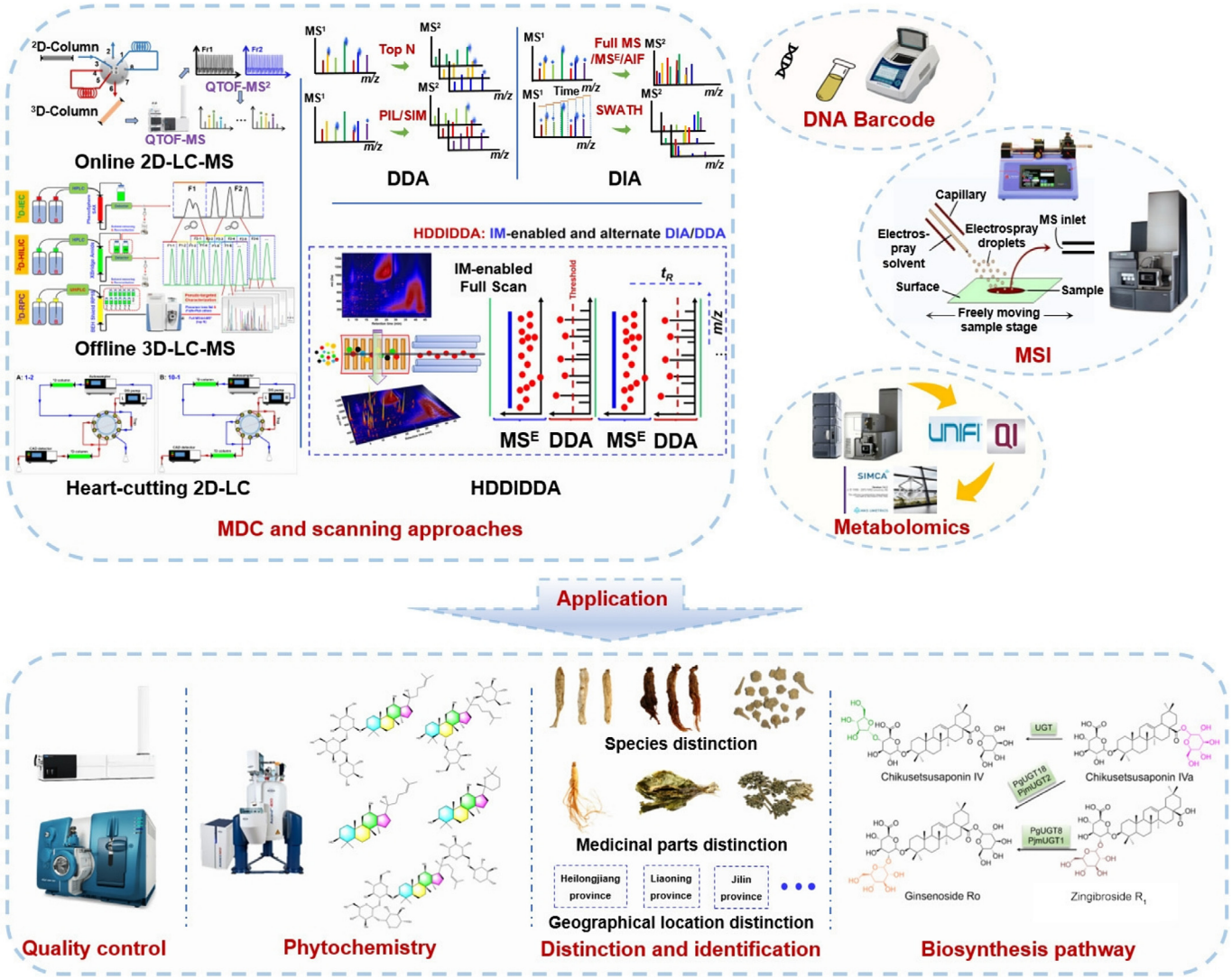


Fig. 3. Technical research and application related to quality control of *Panax* medicinal materials (Jia et al., 2022; Wang et al., 2022a; Xu et al., 2023b).

On-line two-dimensional liquid chromatography (2D-LC) can track the detected components in real time and enable automatic injection on two chromatographic columns, including the heart-cutting 2D-LC (Ma, Ma, Cao, & Wan, 2022; Yang, Jin, Zhang, & Wang, 2023; Yang, Zhang, Zhang, Yang, & Wang, 2022) and comprehensive 2D-LC (Xu et al., 2023a). Selection of the chromatographic columns combination considers not only the separation effect of the ingredients with different chemical properties (such as polarity, acidity and alkalinity) (Ma, Ma, Cao, & Wan, 2022; Yang, Zhang, Zhang, Yang, & Wang, 2022), but also the exerted orthogonality (Xu et al., 2023a; Yang, Jin, Zhang, & Wang, 2023; Yang, Zhang, Zhang, Yang, & Wang, 2022). The loop (Xu et al., 2023a) or trap column (Ma, Ma, Cao, & Wan, 2022) can be configured between the two columns to capture and/or enrich the components for sample loading on the ^{2}D column. Moreover, the solvent strength used in two dimensions of chromatography should be considered, by either introducing a compensation solvent combined with the mobile phase in the ^{2}D chromatography (Ma, Ma, Cao, & Wan, 2022) or using the strength-matching mobile phases (Xu et al., 2023a).

Off-line MDC can avoid the solvent compatibility of the mobile phase, because of the additional step of solvent removal of separated subsamples prior to the injection. Hydrophilic interaction chromatography (HILIC) and reversed-phase chromatography (RPC), showing high orthogonality in separating ginsenosides, can be preferably utilized (Li et al., 2022c). Furthermore, evaluating orthogonality through data modeling based on three descriptors (including the peak occupation rate and system homogeneity in a two-dimensional separation space, as well as the minimal distance among all nearest-neighbor peak distances), effectively improved the efficiency of 2D separation (Sun et al., 2022). Notably, an off-line three-dimensional liquid chromatography (3D-LC) approach was established to separate ginsenosides simultaneously from the flowers of three *Panax* species, in which ion-exchange chromatography (IEC) was used as the ^{1}D chromatography to fractionate between the neutral (e.g., the PPD-, PPT-, and OT-subtype) and the acidic (the OA-subtype and malonylated) ginsenosides, and the resulting neutral and acidic fractions got further fine resolution based on HILIC (^{2}D) and RPC (^{3}D) (Jia et al., 2022).

3.1.2. Mass spectrometry scanning methods

Development of various fit-for-purpose scanning approaches in tandem mass spectrometry can improve resolution, sensitivity, and coverage in detecting the targeted components. In this section, diverse data-dependent acquisition (DDA) and data-independent acquisition (DIA) strategies have been widely applied to the analy-

sis of ginsenosides. By DDA, such as Full MS/dd-MS^2 (Xu et al., 2021a) and the precursor ions list (PIL)-included mode (Yang, Jin, Zhang, & Wang, 2023), the precursors could be automatedly selected according to specific selection criteria for fragmentation, generating highly reliable MS^2 or MS^n spectra for structural identification, because of the narrow selection on the *m*/*z* range. In contrast, DIA can record the secondary fragments of the molecular ions within a certain window range, divided into sequential-window acquisition of all theoretical fragments (SWATH), MS^E (Jiao et al., 2021; Li et al., 2022b; Zhang et al., 2022a), high-definition MS^E (Li et al., 2021b; Liu et al., 2022b; Liu et al., 2023; Mi et al., 2023; Yang et al., 2022), all-ion fragmentation (AIF) (Yu, Yao, & Guo, 2021), and others, according to the size of the mass interval window (Table S2).

In order to overcome the problem of low coverage of the measurement mass range under the single DDA scanning mode, a method of splitting the full scan range into multiple separate segments can be employed to detect components with a large ion mass span (Li et al., 2021d). Typically, by enabling dynamic exclusion (DE) or constructing online mass defect filters (MDF) or the exclusion lists, the fragmentation information for those minor components could be acquired with largely ascending coverage (Li et al., 2021d; Liu et al., 2022a; Sun et al., 2023b). Notably, aimed to explore more unknown ginsenosides, a virtual library of ginsenosides (VLG) involving 13 536 ginsenoside molecules was established using programmed *C* language, and its combination with MDF to create new PIL could assist to discover more new ginsenoside structures from different ginseng varieties (Liu et al., 2022a; Zhang et al., 2022a). In addition, based on the differentiated forms of precursors, integration of MRM-IDA-EPI and MIM-IDA-EPI of the QTrap mass spectrometer was able to identify ginsenosides according to the subtypes (Wang et al., 2023b).

With the inherent merit in coverage, DIA can collect the MS^2 fragments of all the compounds detected by full scan. However, an indispensable deconvolution step, including the ions extraction and matching between the precursor and product ions, is performed to process the available DIA data. The presence of co-eluted components, due to insufficient chromatographic resolution, may result in poor data matching between the MS^1 and MS^2 data. Currently, various metabolomics software, such as DIAMetAlyzer (Alka et al., 2022), DecoID (Stancliffe, Schwaiger-Haber, Sindelar, & Patti, 2021), MetaboAnnotatoR (Graça et al., 2022), and the reported algorithms, spectrum_utils (Bittremieux et al., 2023), tidyMS (Riquelme, Zabalegui, Marchi, Jones, & Monge, 2020), and mummichog algorithm (Rainer et al., 2022), were developed for MS data deconvolution.

In comparison with the use of a single DDA or DIA strategy, the development of hybrid scanning methods becomes a research hot in analytical chemistry. A namely HDDIDDA approach automatedly alternates between DIA and DDA within once injection analysis, which actually combines the advantages of high resolution of ion mobility separation, high spectral quality of DDA, and the high coverage of DIA (Wang et al., 2022a). In particular, a five-dimensional analysis method was established by integrating the HDDIDDA strategy and off-line 2D-LC.

3.1.3. Mass spectrometry imaging

MSI can obtain the multidimensional information of components, such as the mass-to-charge ratio, response intensity, and position distribution in the slice sample. Currently, diverse ionization modes can be utilized in MSI, such as matrix-assisted laser desorption/ionization (MALDI), desorption electrospray ionization (DESI), secondary ion mass spectrometry (SIMS), and laser ablation-inductively coupled plasma (LA-ICP), *etc*. MALDI-MSI and DESI-MSI are the most commonly used techniques amongst them (Lu et al., 2023). Some review articles have introduced the principle of MSI technology with different ionization modes (Granborg, Handler, & Janfelt, 2022; Yoshimura, Goto-inoue, Moriyama, & Zaima, 2016), and the general process of MSI analysis of traditional Chinese medicine was summarized (Li et al., 2022c). In DESI-MSI, the substance is ionized under laser beam irradiation, and the charge is transferred to the sample molecule, causing desorption and ionization of the sample molecules (Jiang et al., 2023; Lu et al., 2023; Granborg, Handler, & Janfelt, 2022; Planque, Igelmann, Campos, & Fendt, 2023).

MSI can visualize the distribution of components and identify differential markers to disclose the variations among different *Panax* species (Huang, Wang, Wang, Chen, & Liu, 2023; Lu et al., 2023), ages (Lu et al., 2023; Wei et al., 2021), medicinal parts (Wei et al., 2021), and processing times (Fan et al., 2022; Sun et al., 2021). In addition, MSI was used to study the distribution of components in *Panax* species (PG, PQ, and PN) (Huang, Wang, Wang, Chen, & Liu, 2023; Wang et al., 2021a) in the biological tissues after entering organisms.

Compared with the LC-MS or GC–MS, MSI can identify the structure and *in situ* distribution without sample extraction (Jiang et al., 2022). However, due to the lack of chromatographic separation, the MS signal obtained by MSI is the result of ion fusion of all isomers. The integration of MSI and LC-MS can provide more useful information in quality control of ginseng.

3.1.4. DNA barcoding

DNA barcoding is a technique for species identification by analyzing one or a few gene fragments. The *pharmacopoeias* of China, USA, Japan, and other nations contain the DNA barcode technology-based method for plant identification, which has been evolving into a powerful quality control method (Linh et al., 2022; Lu et al., 2022). The general steps of DNA barcoding analysis are as follows: (1) isolation of genomic DNA; (2) selection of universal primers and polymerase chain reaction (PCR) amplification; (3) purification and recovery of PCR products; (4) fluorescence quantification of amplification products; (5) Sanger or high-throughput sequencing (HTSeq); and (6) data analysis (Li et al., 2022c). Within the field of plant research, ITS2, psbA-trnH, rbcL, and matK gene fragments, are commonly utilized as detection sequences for the species identification (Chen et al., 2022; Linh et al., 2022; Liu et al., 2021b). DNA sequencing technology has continuously broadened the connotation of plant species identification through ongoing updates and iterations. For example, the species-specific PCR is emerging as an alternative to non-targeted DNA sequencing for species identification of the processed materials (Lu et al., 2022). The DNA mini-barcoding technology features a shorter barcode than the traditional version (less than 300 bp). Moreover, it offers the DNA specificity, high amplification success rates, and efficient identification (Doña et al., 2015). DNA metabarcoding technology, which combines DNA barcoding with HTSeq, can detect multiple species in the combined samples, rendering a potent analytical vehicle in the identification of Chinese patent medicine (Fujii et al., 2021; Liu et al., 2021a; Liu et al., 2021b). Currently, HTSeq, commonly used in the identification of TCM, includes the next generation sequencing (NGS) represented by Illumina series sequencing and third generation sequencing (TGS) represented by PacBio SMRT (single molecule real time, SMRT) sequencing.

DNA barcoding technology has been widely used in the identification of *Panax* plants, and some novel techniques are continuously being reported. Zhang et al. (2021) assessed the efficacy of ITS2 and psbA-trnH DNA barcodes in identifying common ginseng varieties by amplifying genes and distinguishing interspecific differences. Linh et al. (2022) researched the barcodes of chloroplast genes (*trnQ-rps16*, *trnS-trnG*, *petB* and *trnE-trnT*) that were introduced into the identification of seven species of *Panax* and four

other species of medicinal materials. It was found that trnQrps16 was able to classify all the tested evolutionary branches at the species level resolution. Liu et al. (2021b) utilized shotgun DNA metabarcoding technique to precisely identify the *Panax*-containing species in Qingguo Pill and successfully recognized the tagged gene fragments, presenting a unique approach to evaluate the quality of Qingguo Pill. In one study, a high-resolution melting (HRM) method was innovatively added to the DNA barcode, which targeted the gene encoding dammar enediol synthesis enzyme in the ginsenoside biosynthesis pathway and could well distinguish *Panax* species (PG, PQ, PN, PJ, etc.) (Grazina, Amaral, Costa, & Mafra, 2021). In addition, the microorganisms in the cultivation fields of *Panax* (PG and PN) were analyzed based on NGS (Fujii et al., 2021; Shi et al., 2021), providing valuable information for the cultivation.

DNA barcoding offers the advantages of rapid, stable, cost-effective, and precise identification and differentiation of ginseng medicinal materials. However, DNA barcoding alone fails to distinguish different parts of *Panax* species (e.g., roots/rhizomes, leaves, and flowers), and its combination with metabolomic analysis can be very powerful in authenticating ginseng as the raw materials and various products.

3.1.5. Metabolomics

Metabolomics-based strategy is particularly suitable in herbal medicine to holistically unveil the metabolomic difference and identify chemical markers contributing to the discrimination. Metabolomics includes the targeted and untargeted modes, whilst the pseudo-targeted metabolomics integrates the merits of these two modes to pursue high-quality markers (Wang et al., 2023). Plant metabolomics is extensively used in ginseng research to qualitatively and quantitatively analyze the small-molecule metabolites in ginseng from various habitats (Gao et al., 2022; Pang et al., 2023; Yoon, Shin, Oh, Choi, & Young, 2022; Zhang et al., 2023b), different plant parts (Gao et al., 2022; Jiao et al., 2021; Li et al., 2021b; Wang et al., 2022b; Wang et al., 2023b), varieties (Dong et al., 2022; Ji et al., 2023b; Liu et al., 2022b; Nguyen et al., 2023; Wang et al., 2022b; Wang et al., 2023b; Yang et al., 2022), classification grades (Li, et al., 2023a), growth years (Zhang et al., 2022d), and the harvesting and processing methods (Li et al., 2021a; Wei et al., 2023; Zhang et al., 2022c). The general workflows for the metabolomics analysis of ginseng involve the following steps (Fig. 4): (1) sample pretreatment; (2) metabolic feature acquisition (by full scan of HRMS, MRM of tandem mass spectrometry, or GC-MS); (3) data pre-treatment (peak picking, peak alignment, and normalization); (4) multivariate statistical analysis (PCA, HCA, nonlinear mapping, ANN, and OPLS-DA); and (5) identification of chemical markers (e.g., comparison with the reference standards, fragmentation pathways interpretation, and searching of the literature or commercial libraries).

3.2. Application

3.2.1. Multicomponent characterization

The chemical components contained in the *Panax* plants serve as the material basis of ginseng for treating the diseases and quality control. Most of related studies focus on the characterization of ginsenosides by LC-MS, and few concentrated on the polysaccharides (Jia et al., 2021; Lu, Liang, Zhou, Kuang, & Xia, 2021) and volatile oils (Wang et al., 2022b). The head space-solid phase microextraction-gas chromatography-mass spectrometry (HS-SPME-GC/MS) could characterize 259 volatile components simultaneously from 12 ginseng samples including different *Panax* species and different plant parts.

Advanced LC-MS strategies have been developed to characterize ginsenosides in various *Panax* species (Jiao et al., 2021; Li et al., 2021b; Qu et al., 2023) and their different parts (e.g., root/rhizome, stem leaf/leaf, flower, and fruit) (Li et al., 2022a; Li et al., 2021b;

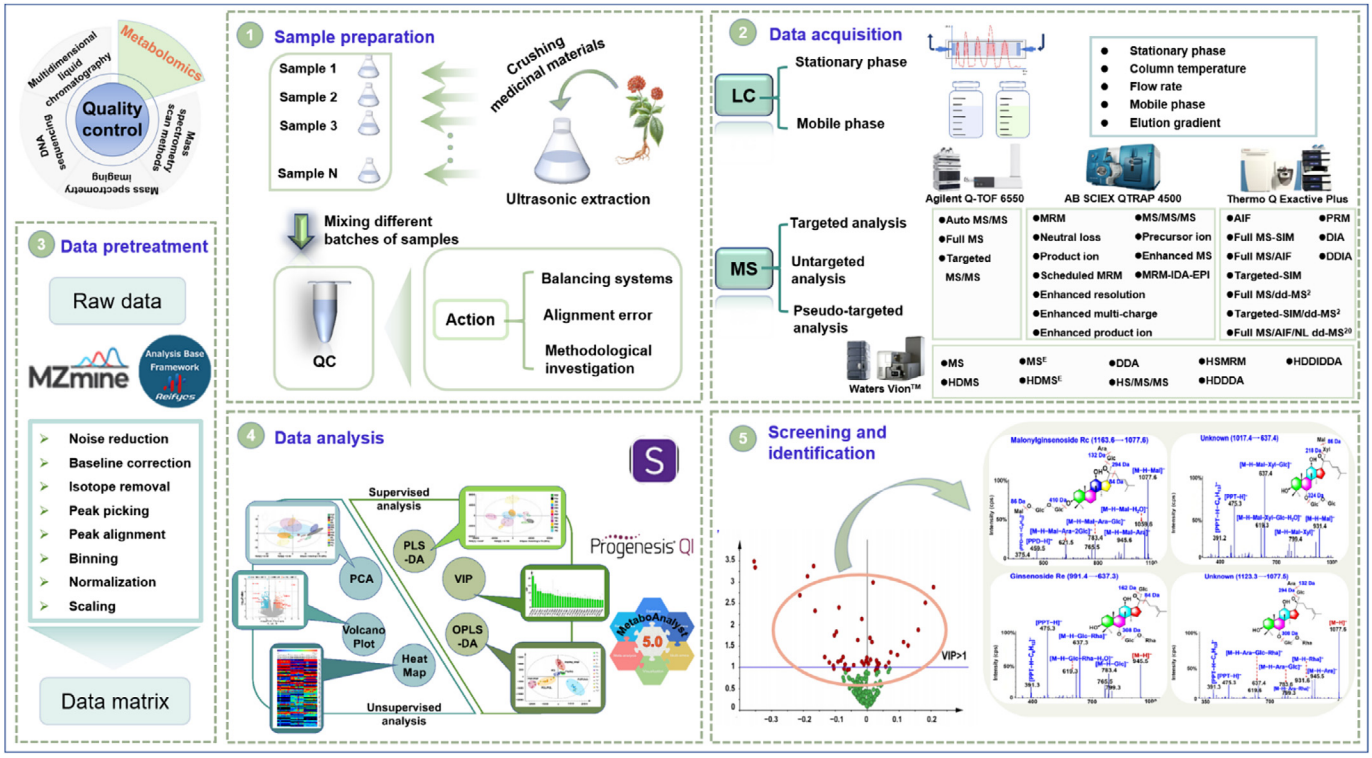


Fig. 4. General flow charts for metabolomics used in quality control of ginseng (Wang et al., 2023b; Yang et al., 2022; Wang et al., 2022b).

Yang et al., 2022; Zhang et al., 2022a). More unknown ginsenosides could be primarily characterized by feat of the enhanced separation dimension of MDC (Qu et al., 2023; Jia et al., 2022; Sun et al., 2023b), the ultra-high resolution of mass spectrometry, and data acquisition methods (Chen et al., 2023; Liu et al., 2022c; Wang et al., 2023a).

From the LC section, Agilent 1200 series HPLC system (Jia et al., 2022; Qu et al., 2023), Ultimate 3000 UHPLC system (Li et al., 2021b; Liu et al., 2022c; Yang et al., 2022; Zhang et al., 2022a), Waters ACQUITY UPLC system (Jiao et al., 2021; Li et al., 2022a), SCIEX ExionLCAD UPLC system (Chen, Zhang, Yang, Xu, & Wang, 2022; Chen et al., 2023; Sun et al., 2023c), and Vanquish™ Flex UHPLC system (Wang et al., 2023a), were used for ginsenosides characterization. Particularly, MDC was able to obtain more ginsenosides from the ginseng extracts (Jia et al., 2022; Qu et al., 2023; Sun et al., 2023b), such as a total of 1 974 ginsenosides from the flowers of PG, PQ, and PN (Jia et al., 2022). In the MS module, various HRMS instruments, such as the Vion IM-QTOF (Li et al., 2021b; Yang et al., 2022), Q Exactive Q-Orbitrap (Jia et al., 2022; Liu et al., 2022c; Zhang et al., 2022a), AB SCIEX Triple TOF 6600 (Chen et al., 2023; Sun et al., 2023c), Orbitrap Exploris 240 (Wang et al., 2023a), and Xevo G2-XS QTOF (Jiao et al., 2021; Li et al., 2022a), were used. Inclusion of PIL in DDA could assist to identify more minor and unknow ginsenosides (Liu et al., 2022c; Zhang et al., 2022a). Based on the UHPLC/Triple TOF-MS/MS platform, DDA in conjunction with DE, MDF, and neutral loss data acquisition functions, was utilized to systematically and comprehensively characterize ginsenosides in the soaked and decocted PG and PQ (Chen et al., 2023). Recently, a novel technique, known as the internal extraction electrospray ionization mass spectrometry (iEESI-MS), was developed to identify the metabolites of PN and PQ, which utilized a flowing energy carrier to transfer energy to a specific area inside the non-broken whole sample, in which the three-dimensional space of the whole sample was extracted into the mobile phase, and energy and charge were obtained from the energy carrier of the mobile phase to convert the neutral molecules into molecular ions (Yuan et al., 2023; Zhang et al., 2022d).

3.2.2. Content determination

Content determination is an important part of the quality standard of TCM, and controlling the content of single or multiple markers is the key to quality evaluation. Some quantitative assay technologies, including UHPLC-UV (Li et al., 2021b; Qu, Wang, Jin, Li, & Wang, 2022), UHPLC-CAD (Xu et al., 2021b), HPLC-DAD (Ji et al., 2023a), UHPLC/Q-Trap-MS (Mi et al., 2022; Qu et al., 2023), UHPLC/Q-Orbitrap-MS (Jia, Hu, Zhu, Yuan, & Zhou, 2021), and UHPLC/QQQ-MS (Zhang et al., 2022c), have been applied to determine the contents of ginsenosides in various herbal medicine or compound formula samples. Viewed by the ginseng varieties, currently available quantitative researches mainly focus on PG, PQ, PN, and their compound preparations (Ji et al., 2023a; Jia, Hu, Zhu, Yuan, & Zhou, 2021; Li et al., 2021b; Qu et al., 2023; Qu, Wang, Jin, Li, & Wang, 2022; Zhang et al., 2022c), while a few were related to PJm (Xu et al., 2021b; Xu et al., 2023a), PJ (Xu et al., 2021b; Xu et al., 2023a), and the other ginseng medicinal materials. In the absence of standard substances, the application of standardized reference extract as a secondary standard can minimize errors related to matrix effects and quantitatively control the quality of medicinal materials (Semenova et al., 2022).

Facing such versatile ginseng varieties, a universal quantitative assay method is highly preferred, which can offer important information for their authentication and differentiation. Based on the excellent performance of CAD, a UHPLC-CAD approach, by using a CORTECS UPLC Shield RP18 column, achieved the simultaneous content determination of 15 ginsenosides to assess the quality of 12 ginseng medicinal materials (Xu et al., 2021b). The same authors developed an on-line heart-cutting 2D-LC/CAD method, by eight continuous cutting and transfer, which enabled the quantitative assay of 16 ginsenosides from 28 different CPMs (Xu et al., 2023b). In another study, a total of 39 ginsenosides in 14 PQ samples were quantified by UFLC-ESI-MS/MS, which achieved the accurate distinction of PQ sourced from China and the United States (Chen, Zhang, Yang, Xu, & Wang, 2022). Moreover, a quantitative study of dencichine in various parts of PN (both in the forest and field environments) using HPLC-DAD, revealed differences in dencichine content among the main roots, fibrous roots, stems, and leaves of PN, as well as in different geographical regions where it was grown (Ji et al., 2023a).

By quantifying the content of ginsenosides during the processing of ginseng, the transition of ginsenosides can be unveiled, which is utilized for quality control in the production and processing of ginseng products. The ginsenoside contents of various PG varieties, including the raw materials and transformed samples, were compared after undergoing the heating and acid treatment, with 18 ginsenosides simultaneously quantified using an HPLC-UV approach (Zhang et al., 2021). In another study, various types of ginsenosides were converted into their corresponding aglycones by the acid hydrolysis and alkali hydrolysis, and a rapid and straightforward quantitative method for total ginsenosides was established (Abashev, Stekolshchikova, & Stavrianidi, 2021).

3.2.3. Distinction and identification

In the authentication and identification of various *Panax* plants, various technologies, such as LC-MS, MDC, DNA sequencing, and MSI, were used to comprehensively characterize and compare the ginsenosides, polysaccharides, volatile oils, and some primary metabolites.

The types and contents of ginsenosides are determined by metabolomics comparison or quantitative assay, which are diagnostic for distinction among different *Panax* species and the different plant parts within the same species. Notoginsenoside R_1 (noto-R1), majonoside R_1, vinaginsenoside R_{14}, ginsenoside Rf, and ginsenoside Rd, were reported as the marker compounds to distinguish five ginseng species: PG, PQ, PN, PJ, and PJm (Ji et al., 2023b). Quantitative analysis of the roots, stems, and leaves of PN in Yunnan showed that the content of PPD-type ginsenosides in leaves was higher than that in the roots and stems, while the PPT-type ginsenosides were more abundant in the roots and stems (Gao et al., 2022). Floralginsenoside P or its isomer was identified as a new potential marker for distinguishing the leaves and flower buds of PN (Li et al., 2021b). The ratio of the peak area for some ginsenoside markers can be used to distinguish different parts from the same *Panax* plant (Wang et al., 2023b). Aside from the commonly used LC-MS-based metabolomics differential analysis, a three-dimensional characteristic chromatogram concept was presented by online 2D-LC/UV monitoring of 17 known ginsenoside markers (Xu et al., 2023a). Compared to PQ from China, the PQ from North American had lower levels of the PPD-type ginsenosides, while the PPD-type ginsenosides with four glucose groups were much higher (Pang et al., 2023). Due to the impact of growth environment stress, the types and contents of ginsenosides synthesized by *Panax* species show significant differences. Consequently, these variations contribute to the diverse physiological effects and pharmacological quality observed in the plants. Ginsenosides Rg_1, -Re, -Rb_1, -Rc, -Rb_2, and -Rg_3, can be used as the pharmacological identification markers for the hepatoprotective effects of garden and mountain PG (Li et al., 2021a).

The role of polysaccharides in the precise quality control of ginseng has been investigated. By utilizing a three-level fingerprint (e.g., the polysaccharides, partially hydrolyzed oligosaccharides, and completely hydrolyzed monosaccharides) combined with untargeted metabolomics differential analysis, the composition

and content differences of the polysaccharides including the total polysaccharides and the non-starch polysaccharides in PG, RG, PQ, PN, PJ, and PJm were explored and compared at three levels (Liu et al., 2022b; Liu et al., 2023). Especially, some oligosaccharide markers showed potential significance in distinction of RG and PN from the other ginseng varieties. The significance of oligosaccharides in discriminating different ginseng species deserves more profonde studies, which is beneficial to the precise quality control of ginseng.

4. Biosynthesis pathway

In the realm of ginseng biosynthesis, ginsenoside undoubtedly takes the center stage. It is widely recognized that ginsenoside biosynthesis occurs via the methylerythritol phosphate (MEP) pathway and the mevalonate (MVA) pathway (Fig. 5).

4.1. Generation of isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP)

Squalene is derived from the condensation of isopentenyl pyrophosphate (IPP or IDP) and 3,3-dimethylallyl diphosphate (DMAPP or DMADP). Compared to the MEP pathway, the MVA pathway plays a more significant role (Luthra, Roy, Pandit, & Prasad, 2021). HMG-CoA reductase (HMGR) is a pacemaker enzyme involved in the MVA pathway, and its expression positively controls the production of ginsenosides in *Panax* (Hou, Wang, Zhao, & Wang, 2021).

4.2. 2,3-Oxidosqualene

It has been reported that 2,3-oxidosqualene is a monooxidation product of squalene oxidized by squalene epoxidase (SE). Squalene is synthesized from two farnesyl diphosphate (FPP) molecules through the squalene synthase (SS), in which FPP is formed by farnesyl pyrophosphate synthase (FPS) catalyzing the addition of two IPP molecules to DMAPP to obtain geranyl diphosphate (GPP) and then reacting again (Hou, Wang, Zhao, & Wang, 2021; Mohanan, Yang, & Song, 2023).

4.3. Cyclization and on-ring modification of 2,3-oxidosqualene

After cyclization of 2,3-oxidosqualene with the oxidosqualene cyclase (OSC), various triterpenoid saponin skeletons (e.g., PPD, PPT, OT, oleanane, dammarenediol, and sterols, *etc.*) are produced. At present, four types of OSCs, including the cyclotenol synthase (CAS), lanosterol synthase (LAS), β-amyrin synthase (β-AS), and dammarenediol synthase (DDS), were identified in ginseng (Li et al., 2023b). Related studies demonstrated that the expression of OSCs in different species might be influenced by their respective growing environments (Koo et al., 2023).

4.3.1. Sterols

Phytosterols are the crucial structural components of cell membranes. Cyclotenol and lanosterol are synthesized through the cyclization of 2,3-oxokeratin under the catalysis of LAS or CAS (Li et al., 2022c; Li et al., 2023b).

4.3.2. PPD-type

Dammarenediol-II synthase (DS), protopanaxadiol synthase (PPDS), and cytochrome P450 reductase (CPR) were used to create the yeast strains capable of generating PPD ginsenosides. DDS cyclized 2,3-oxidosqualene via DS to form dammarenediol-II (DM), which could then be oxidized to produce PPD and PPT (Hou, Wang, Zhao, & Wang, 2021).

During the study of *Panax* plants, approximately 20 CYP450s were found. Only three CYP450s have been characterized as being related to ginsenoside synthesis, including CYP716A47 (protopanaxadiol synthase-PPDS), CYP716A53v2 (protopanaxatriol synthase-PPTS), and CYP716A52v2 (oleanolic acid synthase-OAS) (Hou, Wang, Zhao, & Wang, 2021; Mohanan, Yang, & Song, 2023). CYP716A47 could hydroxylate at the DM site to produce PPD, while glycosyltransferases (GTs) catalyzed the production of other forms of PPD-type ginsenosides (Li et al., 2022c).

4.3.3. PPT-type

Protopanaxadiol can produce protopanaxatriol through PPTS alcoholization. It was found that overexpressing of PPTS gene can regulate the production of PPD-type ginsenosides, indicating an antagonistic relationship between these two subtypes in ginsenosides production (Mohanan, Yang, & Song, 2023). Other types of PPT, which are similar to PPD-type ginsenosides, are also produced through glycosylation by GTs.

4.3.4. OT-type

Natural OT-type ginsenosides are rare. The researchers explored the following strategies for producing the OT-type ginsenosides (Niu, Luo, Lv, & Lu, 2021). 1) converting the oxidative side chain to OT-type ginsenosides; 2) synthesizing by acylation of the PPD- or PPT-type ginsenosides, followed by the side chain oxidation and cyclization, and then deacylation; and 3) substituting pseudo-ginsenoside DQ on 3-OH to obtain 3-substituted OT-type triterpene derivatives.

4.3.5. Oleanane-type

In addition to the dammarane ginsenoside, oleanane can be generated by altering β-amyrin, a product of 2,3-oxidized shark, which is cyclized by β-AS (Tang et al., 2021).

4.3.6. Dammarenediol-type

Following the cyclization reaction catalyzed by DDS, 2,3-squalene undergoes a "chair-chair-chair" structural change, forming the basic structure of dammarenediol. Subsequently, a series of GTs play an important role in the further transformation of the dammarenediol-type ginsenosides.

Ginsenoside synthesis is intimately tied to specific enzymes found in the living organisms. Therefore, it is often inferred that the production, content, and types of ginsenosides are regulated by affecting the concentration of enzymes. UDP-glycosyltransferases (UGTs) and/or acyltransferase in PN and PG were characterized, which could catalyze the transformation of major ginsenosides into the minor ginsenosides (Li et al., 2021c; Lin et al., 2023). Researchers isolated a new glycoside hydrolase (BglNar) from deep sediments, which was capable of converting major ginsenosides into ginsenoside F2 (Siddiqi et al., 2021).

The typical mode of triterpene glycosylation is to link 2–5 monosaccharide-oligosaccharide chains to C-3 and C-28. The yield of ginsenoside is affected by deglycosylation and hydrolysis catalyzed by β-glucosidase, pectinase, and other glycosidases, with β-glucosidase being the best hydrolase for glycosidic bonds on ginsenoside (Chu, Huy, & Tung, 2023; Tran et al., 2023). Several studies had looked into how high hydrostatic pressure (HHP), enzymatic hydrolysis, and ultrasonic extraction on enhancing the yield of the major and minor ginsenosides in wild simulated ginseng (WSG). The concentration of ginsenosides significantly increased when treated with HHP+Pectinex-soni (Mok, Jung, Kim, & Kim, 2023). In addition to interfering with biosynthesis by affecting enzymes, the application of elicitors including synthetic products, abiotic elicitors, biological elicitors, etc. has a significant influence on the yield of ginsenosides (Hou, Wang, Zhao, & Wang, 2021; Luthra, Roy, Pandit, & Prasad, 2021).

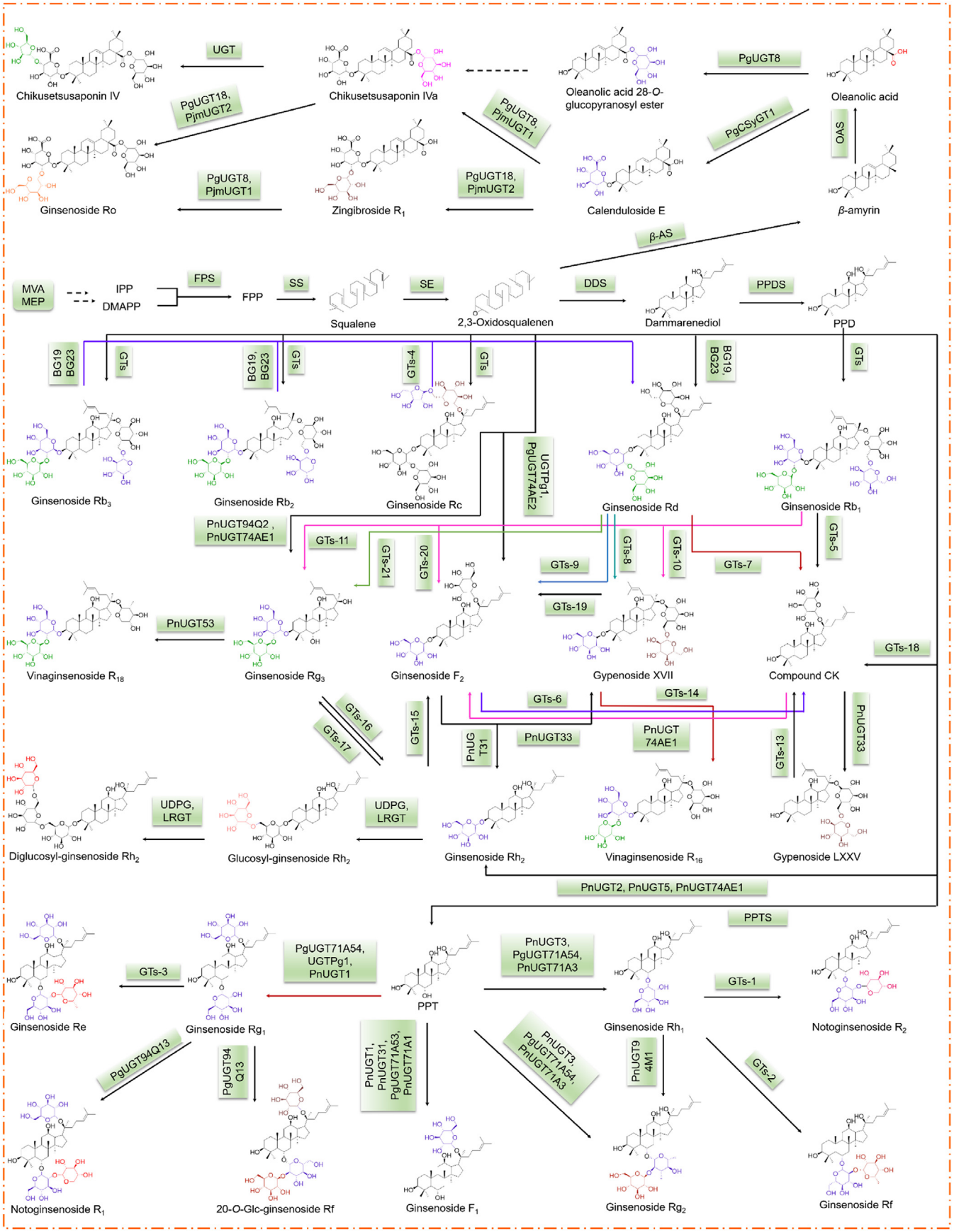


Fig. 5. Biosynthetic pathways of different types of ginsenosides from MVA pathway and MEP pathway.

Some researchers had effectively inhibited the biosynthesis of lanosterol through ERG7 mediated by dCas9-sgRNA, potentially enhancing the production of PPD-type ginsenosides in strains (Lim et al., 2021). By combining the A-ring of dammarane ginsenoside with a nitrogen-containing heterocyclic ring, derivatives of dammarane ginsenoside were successfully obtained. These derivatives could trigger the apoptosis in cancer cells by regulating the expression of apoptosis-related proteins and activating the caspase cascade reaction (Ma et al., 2021).

5. Summary and prospects

As highly valued Chinese herbal medicines with both the medicinal and food properties, various ginseng species have been attracting the global concerns and are extensively consumed. This review gives a comprehensive summary of the phytochemistry, quality control, and biosynthesis of ginseng in the past three years. Undoubtedly, remarkable progress is achieved by feat of the ongoing development of analytical technologies, which assist in the rapid discovery and isolation of novel ginsenoside compounds and polysaccharides, as well as the more reliable authentication of both the ginseng drug materials and versatile ginseng-containing products. It is thus believed that the integration of multiple and multi-faced analytical techniques can enable practical solutions to those obstacles encountered in the modern researches of ginseng.

However, we're also aware of the challenges in ginseng research that deserve more investigations in the future. i) We're still in lack of the potent approaches that can enable the efficient discovery and accurate identification of new ginsenosides; ii) the analytical strategy for the precise authentication and differentiation of the similar ginseng species is insufficient, especially to identify them in the compound preparations; iii) potential benefits and the action mechanism of ginseng polysaccharides should be further exploited; and iv) the chemical basis underlying the differentiated properties and clinical use of different ginseng (according to the TCM theory) remains unclear. Future efforts can include integrating MDC-MS and machine learning-based structure information prediction such as the retention time and ion mobility-derived CCS to accurately identify those minor or even trace new ginsenoside structures, combining DNA sequencing and metabolite markers to precisely authenticate the ginseng species, and the merging of multidisciplinary investigations to unveil the distinct features of multiple ginseng.

CRediT authorship contribution statement

Mengxiang Ding: Investigation, Writing – original draft. **Huizhen Cheng:** Writing – original draft. **Xiaohang Li:** Writing – original draft. **Xue Li:** Validation. **Min Zhang:** Writing – original draft. **Dianxin Cui:** Software. **Yijin Yang: Xiaojin Tian:** Data curation. **Hongda Wang:** Validation, Writing – review & editing. **Wenzhi Yang:** Funding acquisition, Project administration, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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