Review Article

Phytochemical analysis of Panax species: a review

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A B S T R A C T

Panax species have gained numerous attentions because of their various biological effects on cardiovascular, kidney, reproductive diseases known for a long time. Recently, advanced analytical methods including thin layer chromatography, high-performance thin layer chromatography, gas chromatography, high-performance liquid chromatography, ultra-high performance liquid chromatography with tandem ultraviolet, diode array detector, evaporative light scattering detector, and mass detector, two-dimensional high-performance liquid chromatography, high speed counter-current chromatography, high speed centrifugal partition chromatography, micellar electrokinetic chromatography, high-performance anion-exchange chromatography, ambient ionization mass spectrometry, molecularly imprinted polymer, enzyme immunoassay, 1H-NMR, and infrared spectroscopy have been used to identify and evaluate chemical constituents in Panax species. Moreover, Soxhlet extraction, heat reflux extraction, ultrasonic extraction, solid phase extraction, microwave-assisted extraction, pressurized liquid extraction, enzyme-assisted extraction, acceleration solvent extraction, matrix solid phase dispersion extraction, and pulsed electric field are discussed. In this review, a total of 219 articles published from 1980 to 2018 are investigated. Panax species including P. notoginseng, P. quinquefolius, sand P. ginseng in the raw and processed forms from different parts, geographical origins, and growing times are studied. Furthermore, the potential biomarkers are screened through the previous articles. It is expected that the review can provide a fundamental for further studies.

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1. Introduction

Genus Panax belonging to Family Araliaceae contains eleven species (three varieties) namely P. trifolius, P. notoginseng, P. quinquefolius, P. ginseng, P. pseudoginseng, P. zingiberensis, P. stipuleanatus, P. japonicus, P. japonicus var. angustifolius, P. japonicus var. major, and P. japonicus var. bipinnatifidus, which are mainly distributed in the Eastern Asia and Northern America [1]. Among them, most of the investigations have been conducted on P. notoginseng, P. quinquefolius, and P. ginseng for their pharmacological activity. Their use to treat cardiovascular, kidney, and reproductive diseases has a long history [2]. Various bioactive constituents including ginsenosides, polysaccharides, alkaloids, glucosides, and phenolic acids have been identified in P. ginseng in a previous study [3]. The main ginsenosides isolated from Panax species are shown in Fig. 1. They contain protopanaxadiol, protopanaxatriol, ocatillo, oleanolic acid, and C-17 side chain type [4,5]. Protopanaxadiol has a glucose moiety attached to C-20 and C-3, and protopanaxatriol has glycosylation sites at C-20, C-3, and C-6. The cleavage of glucose bond at C-20 is hydrolyzed before bond at C-3 and C-6 in processed condition [6]. The amount of isomer pairs is detected, and 20(5)-ginsenosides are always eluted more easily than 20(R)-ginsenosides [6]. Moreover, Δ20(21) ginsenosides are eluted before their Δ20(22) derivatives. Ocatillo-type and oleanane-type have a side chain at C-20. Yao et al have identified 945 ginsenosides from P. notoginseng leaves and 662 potentially novel ginsenosides [7]. Various species, parts, processings, regions, and growing times have a great influence on the chemical compounds of herbal medicines.

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Fig. 1. The main ginsenosides of *Panax* species (protopanaxadiol, protopanaxatriol, ootitollol, oleanane, and C-17 side chain type).
In the previous review, chemical and pharmacological diversity of ginsenosides of genus *Panax* L. was summarized [4,8,9]. Wang et al (2015) reviewed analytical techniques that were used in the evaluation of *P. quinquefolius*, while some advanced methods such as 2D-HPLC, micellar electrokinetic chromatography, and high-performance anion-exchange chromatography (HPAEC) were not investigated. In addition, *P. ginseng* and *P. notoginseng* with phenolic acids, dencichines, trilinoleins, flavonoids, and vitamins were not described [10]. Qi et al (2011) reviewed preparation, analytical advance, and applications of ginseng from January 2000 to September 2010 [11]. However, there are only few investigations in which analytical methods were applied to evaluate *Panax* species. Some advanced techniques such as ambient ionization mass spectrometry are hardly described in previous studies. In this review, we analyzed the published phytochemical analysis of *Panax* based on the keywords “Panax, ginseng” from Pubmed and Google Scholar. A total of 219 articles from 1980 to 2019 in the analytical methods of *Panax* species were investigated. As shown in Fig. 2, it is found that few researches are conducted during 1980 and 2000. The number of papers gradually grows with the time. It increased rapidly after 2011. Different sample preparations have significant influence on analysis of the bioactive compounds. The different analytical methods have different performances on the analysis of constituents of *Panax* species. Analytical methods including thin layer chromatography (TLC), high-performance thin layer chromatography (HPTLC), gas chromatography (GC), high-performance liquid chromatography (HPLC), ultra-high performance liquid chromatography (UHPLC) with tandem ultraviolet (UV) detector, diode array detector (DAD), evaporative light scattering detector (ELSD), and mass detector, two-dimensional high-performance liquid chromatography (2D-HPLC), ambient ionization mass spectrometry, high speed counter-current chromatography (HSCCC), and high speed centrifugal partition chromatography (HPCPC) are investigated. Furthermore, the methods have been applied to raw and processed ginseng of different species, from different parts, regions, growing ages, and biochemical analysis. The application in various fields is to screen the potential biomarkers for evaluating and quality control of *Panax* species. It is expected that the current review would have a solid fundamental for the future investigation.

### 2. Sample preparations

During isolation and purification of bioactive components from natural products, extraction is the first and essential step [12]. A method with short extraction time, less extraction solvent, simple operation, low cost, and high extraction efficiency could be accepted. Sometimes many of factors are not satisfied because of the chemical profile of medicinal plants. In this review, the factors of sample preparations for *Panax* species are discussed (Table 1). As a traditional method, heat reflux extraction is used to extract ginsenosides, while it has the disadvantages of chemical transformation, wasting extraction solvent, and complicate operation [13]. Owing to convenient, simple, and high-efficient extraction, various extraction solvents (different concentrations of ethanol and methanol) and times have been used to extract ginsenosides, polyacetylenes, phenolic acids, flavonoids, and so on [14–16]. The operation time of microwave-assisted extraction is 60 times more efficient than that of Soxhlet extraction and 20 times more efficient than that of ultrasonic extraction [17]. Moreover, malonylginsenosides Rb1, Rc, Rb2, and Rd can transform into corresponding neutral ginsenosides Rb1, Rc, Rb2, and Rd under high pressure microwave-assisted extraction at 400 kPa in 70% ethanol—water and at 600 kPa in methanol [18]. Compared with Soxhlet extraction, heat reflux extraction, ultrasonic extraction, and microwave-assisted extraction, pressurized liquid extraction has the highest extraction efficiency in the shortest time for *P. quinquefolius*, *P. notoginseng*, and red ginseng [12,19,20]. The amount of total ginsenosides (Rb1, Rb2, Rc, Rd, Re, and Rg1) increased with ultra-high-pressure extraction, whereas pressuring level and time have no influence on the content of ginsenosides [21]. The extraction time of pulsed electric field is less than 1 s, which is much less than that of heat extraction method (6 h) [22]. In addition, matrix solid phase dispersion extraction has the advantages of short extraction time and less solvent usage, when compared with reflux extraction [23].

### 3. Analytical methods

In the previous study, chromatographic methods including TLC/ HPTLC, GC, HPLC, UHPLC (UV detector, DAD, ELSD, and MS

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**Table 1**

| Technology                           | Extraction Time | Extraction Solvent | Extraction Efficiency | Operation | Cost | Reference |
|--------------------------------------|-----------------|--------------------|-----------------------|-----------|------|-----------|
| Soxhlet extraction                   | Long            | More               | High                  | Moderate  | Low  | [13]      |
| Heat reflux extraction               | Long            | More               | High                  | Moderate  | Low  | [125]     |
| Ultrasonic extraction                | Moderate        | Moderate           | High                  | Simple    | Moderate | [126]    |
| Solid phase extraction               | Long            | Moderate           | Moderate              | Simple    | Moderate | [127]    |
| Microwave-assisted extraction        | Short           | Less               | High                  | Simple    | High  | [17]      |
| Pressurized liquid extraction        | Short           | Less               | High                  | Simple    | High  | [128]     |
| Enzyme-assisted extraction           | Long            | Less               | Low                   | Complex   | Low   | [113]     |
| Accelerated solvent extraction       | Short           | Less               | High                  | Simple    | High  | [129]     |
| Matrix solid phase dispersion extraction | Short         | Less               | High                  | Simple    | Moderate | [23]   |
| Pulsed electric field                | Short           | More               | High                  | Simple    | Moderate | [22]    |

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Fig. 2. The number of papers published during 1980 and 2019.
detector), 2D-HPLC, HSCCC/HPCPC, and spectroscopic analysis, e.g., near infrared (NIR) spectroscopy and NMR, have been used to evaluate Panax species. Moreover, some advanced techniques such as ambient ionization mass spectrometry are applied to Panax. It is obvious that different techniques show different advantages and shortcomings. Detailed comparisons are provided in Table 2.

3.1. TLC/HPTLC

As a rapid qualitative and quantitative analysis technology, TLC is recorded by Chinese Pharmacopoeia. Some scholars have applied TLC to evaluate Panax species (Table 3). In P. ginseng, ginsenosides Rb1, Rb2, Rc, Rd, Re, and Rg1 are determined simultaneously by HPTLC at an absorption of 275 nm. The method consists of a quaternary-solvents system (1,2-dichloroethane–100% ethanol–methanol–water, 56.8:19.2:19.2:4.8) to have an efficient saponins recovery and selective separation [24]. Different species with free mono- and oligo-saccharides are identified by HPTLC [25].

Moreover, to determine ginsenosides in P. trifolius, 2D-TLC with eluent A (chloroform–methanol–ethyl acetate–butanol–water, 4:4:8:1:2), eluent B (chloroform–butanol–methanol–water, 4:8:3:4), and eluent C (chloroform–methanol–water, 13:7:2) were used [26].

Table 2
The advantages and shortcomings of technique analysis for Panax species

| Technique                  | Advantages                                      | Shortcomings                                    | Reference   |
|----------------------------|-------------------------------------------------|-------------------------------------------------|-------------|
| TLC/HPTLC                  | Rapid analysis                                  | Bad efficiency in separation                    | [24–26]     |
|                            | Convenient operation                            | Bad stability                                   |             |
|                            | High sensitivity and specificity                 | Need volatile organic solvents                  |             |
|                            | Low cost                                        | Low accuracy in quantification                  |             |
| GC                         | Rapid analysis                                  | Limited to volatile compounds                   | [76,130]    |
|                            | Less solvent consuming                          | Operation with the derivatization               |             |
|                            | High sensitivity                                | High cost                                       |             |
|                            | Less time analysis                               |                                                 |             |
| HPLC/UHPLC                 | Convenient operation                            | Long analysis time                              | [131–133]   |
| UV/DAD                     | High specificity                                | Large solvent consuming                         |             |
|                            | High repeatability                              | Analytes with ultraviolet absorption            |             |
|                            | Low cost                                        | Low sensitivity                                 |             |
| ELSD                       | High specificity                                |                                                 |             |
|                            | Low cost                                        |                                                 |             |
| MS                         | Convenient operation                            | High cost                                       | [93,134,135]|
|                            | High sensitivity                                |                                                 |             |
|                            | Less solvent consuming                          |                                                 |             |
|                            | High resolution                                 | Bad stability                                   |             |
| 2D-LC                      | Wide coverage                                   | Complicated operation                           | [55,56]     |
|                            | Good orthogonality                              |                                                 |             |
|                            | High efficiency in separation                   | Large solvent consuming                         |             |
| Ambient ionization mass spectrometry | Rapid analysis                              | Bad stability                                   | [58]        |
|                            | Convenient operation                            | High cost                                       |             |
|                            | Less solvent consuming                          | Low sensitivity                                 |             |
|                            | High resolution                                 |                                                 |             |
| HSCCC/HPCCC                | High efficiency in separation                   | More solvent consuming                          | [62,136]    |
| 1H NMR                     | Fast analysis                                   | High cost                                       | [65,66]     |
|                            | Less solvent consuming                          | Low accuracy in quantification                  |             |
|                            | Easy operation                                  |                                                 |             |
| Near infrared              | Fast analysis                                   | Low accuracy in quantification                  | [137,138]   |
|                            | No solvent consuming                            |                                                 |             |
|                            | No sample preparation                           |                                                 |             |
|                            | Low cost                                        |                                                 |             |

Table 3
Chemical analysis of Panax species by TLC/HPTLC

| Method      | Species                  | Part | Analytes                  | Reference |
|-------------|--------------------------|------|----------------------------|-----------|
| HPTLC       | P. ginseng               | Root | Ginsenosides Rb1, Rb2, Rc, Rd, Re, Rg1 | [24]      |
| HPTLC       | P. ginseng, P. quinquefolius, P. notoginseng | Root | Glycome | [25] |
| 2D-TLC      | P. trifolius             | Root | Ginsenosides Ro, Rb1, Rb2, Rc, Rd, Re, Rg1, Rg2 | [26] |

Table 4
Chemical analysis of Panax species by GC–MS

| Method      | Species                  | Part | Analytes                  | Reference |
|-------------|--------------------------|------|----------------------------|-----------|
| GC–MS       | P. ginseng               | Root | Ginsenosides Rg1, Re, Rd, Rc, Rb1, F1 | [30]      |
| GC–MS       | Panax genus              | Root | Panaxynol and panaxydol    | [139]     |
| GC–MS       | P. ginseng               | Root | Phenolic acids             | [31]      |
| GC–MS       | P. notoginseng           | Root | Dencichine                 | [32]      |
| GC–MS       | P. ginseng               | Root | Volatile organic compounds | [76]      |
| GC–MS       | P. notoginseng           | Root | Volatile organic compounds | [130]     |
| GC–MS       | P. ginseng, P. notoginseng, P. quinquefolius | Root | Volatile organic compositions | [29] |
| GC–MS       | P. ginseng, P. quinquefolius, P. notoginseng | Root | Volatile organic compounds | [140] |
| Method     | Species                  | Part                        | Analytes                                                                 | Reference |
|-----------|--------------------------|-----------------------------|--------------------------------------------------------------------------|-----------|
| HPLC-UV   | *P. ginseng*             | Root                        | Ginsenosides Rb1, Rb2, Rc, Rd, Rg1, Re, Rf                               | [141]     |
| HPLC-UV   | *P. ginseng*             | Different parts and ages    | Ginsenosides Rg5, Re, Rb1, Rc, Rb2, Rb3, Rd                              | [102]     |
| HPLC-UV   | *P. ginseng*             | Root                        | Ginsenosides Rg5, Re, Rb1, Rc, Rb2, Rd                                  | [22]      |
| HPLC-UV   | *P. ginseng*             | Leaf                        | Ginsenosides F1, F2, F3, Re, Rg1, Rd, Rc, Rb2                             | [23]      |
| HPLC-UV   | *P. ginseng*             | Root                        | Ginsenosides Rg2, Rg3, Rg5, Rg6, Rh1, Rha, Rk1, Rk2, Rk3, F1, F4        | [73]      |
| HPLC-UV   | *P. ginseng*             | Root                        | Ginsenosides Rg5, Re, Rb1, Rd                                           | [142]     |
| HPLC-UV   | *P. ginseng*             | Root                        | Ginsenosides Rb1, Rb2, Rc, Rd, Rf, Rg1, Rg2, Rg5, Rg6, Rh1, Rha, Rk1, F1, F4 | [131]     |
| HPLC-UV   | *P. ginseng*             | Root                        | Ginsenosides Rg5, Re, Rb2, Rc, Rd, Rf, Rg1, Rg2, Rg5, Rg6, Rh1, Rha, Rk1, F1, F4 | [143]     |
| HPLC-UV   | *P. ginseng*             | Root                        | Malonyl ginsenosides                                                    | [144]     |
| HPLC-UV   | *P. ginseng*             | Root                        | Ginsenosides and phenolic                                               | [145]     |
| HPLC-UV   | *P. quinquefolius*       | Root                        | Ginsenosides Rg5, Re, Rb1, Rc, Rb2, Rd                                 | [132]     |
| HPLC-UV   | *P. quinquefolius*       | Leaf, stem, root            | Ginsenosides Rg5, Re, Rf, Rb1, Rc, Rb2, Rd                              | [125]     |
| HPLC-UV   | *P. quinquefolius*       | Root                        | Ginsenosides Rb1, Rb2, Rc, Rd, Re, Rg1, and F2, gypenoside XVII         | [43]      |
| HPLC-UV   | *P. quinquefolius*       | Root                        | Ginsenosides Rg5, Re, Rb1, Rd                                           | [17]      |
| HPLC-UV   | *P. quinquefolius*       | Root                        | Ginsenosides Rg5, Re, Rb1, Rc, Rd, Re, Rf, Rg1                           | [146]     |
| HPLC-UV   | *P. quinquefolius*       | Root                        | Ginsenosides Rg5, Re, Rb1, Rc, Rd                                       | [147]     |
| HPLC-UV   | *P. quinquefolius*       | Root                        | Ginsenosides Rb1, Rb2, Rc, Rb2, Rd, Rg1                                 | [113]     |
| HPLC-UV   | *P. quinquefolius*       | Different parts and ages    | Ginsenosides Rg5, Re, Rb1, Rc, Rb2, Rd                                  | [42]      |
| HPLC-UV   | *P. quinquefolius*       | Root                        | Rare ginsenosides 20(S/R)-Rh1, Rg2, F4, 20(S/R)-Rg6, Rk1, Rg4          | [148]     |
| HPLC-UV   | *P. notoginseng*         | Root                        | Notoginsenoside R1, ginsenosides Rg5, Rb1, Rd                           | [133]     |
| HPLC-UV   | *P. notoginseng*         | Root                        | Notoginsenoside R1, ginsenosides Rg5, Rb1, Rd                           | [127]     |
| HPLC-UV   | *P. notoginseng*         | Root                        | Notoginsenoside R1, ginsenosides Rg5, Rb1, Rd                           | [119]     |
| HPLC-UV   | *P. notoginseng*         | Rat tissue                  | Ginsenosides Rg5, Re, Rb1, Rd                                          | [149]     |
| HPLC-UV   | *P. notoginseng*         | Flower bud                  | Notoginsenoside R1, ginsenosides Rg5, Re, Rb1, Rb2, Rd, F2              | [150]     |
| HPLC-UV   | *P. notoginseng*         | Different parts             | Notoginsenoside R1, ginsenosides Rb1, Rb2, Rd, Re, Rg1, Rb2, Rg2, Rg3, Rh1 | [110]     |
| HPLC-UV   | *P. notoginseng*         | Root                        | Notoginsenoside R1, ginsenosides Rg5, Rb1, Rd                           | [151]     |
| HPLC-UV   | *P. notoginseng*         | Root                        | Ginsenosides Rg5, Re, Rb1, Rd, notoginsenoside R1                       | [152]     |
| HPLC-UV   | *P. notoginseng*         | Root, leaf, stem            | Ginsenosides Rg5, Re, Rb1, Rd, notoginsenoside R1                       | [153]     |
| HPLC-UV   | *P. notoginseng*         | Root                        | Notoginsenoside R1, ginsenosides Rg5, Re, Rb1, Rd                       | [154]     |
| HPLC-UV   | *P. notoginseng*         | Root, rhizome               | Notoginsenoside R1, ginsenosides Rg5, Rb1, Rd, Re, quercetin            | [133, 156]|
| HPLC-UV   | *P. ginseng, P. quinquefolius, and ginseng drug preparations* | Different parts             | Ginsenosides Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, Rg2, Rg5, Rg6, Rh1, Rha, Rk1, F1, F4 | [41]      |
| HPLC-UV   | *P. sokpayensis, P. bipinnatifidus* | Rhizomes                  | Ginsenosides Rg5, Rg6, Re, Rf, Re, Rd, Rc, Rb1, Rb2                     | [95]      |
The TLC technology has some advantages of rapid, convenient, and sensitive characteristics to target compounds, whereas it always needs standards and there is a lack of uniqueness for bioactive compounds. In recent years, HPTLC-MS with rapid and accurate profile will hope for evaluating Panax species [27]. Two-dimensional HPTLC showed an efficient performance and good isolation profiles for Panax species in another study [28].

### 3.2. Gas chromatography

Gas chromatography is employed to determine volatile organics, ginsenosides, and phenolic acids from Panax species (Table 4). Different derivatizations for chemical components were selected. For volatile organics, the GC–MS method can determine bioactive compounds of headspace without sample preparation for discriminating Panax species [29]. When determining ginsenosides in *P. ginseng*, it is applied to high-molecular-weight saponins after derivatization with trimethylsilylation [30]. Sample is subjected to trimethylsilylare derivatization for evaluating phenolic acids in white and red ginsengs [31]. After derivatization with ethyl chloroformate, dencichine or other amino acids of *P. notoginseng* are determined [32]. GC–MS for volatile components can take some advantage with simple, fast, and effective characters, whereas for some non-volatile components, a complex operation is required. 2D-GC with high peak capacity, orthometric characteristic can be used to evaluate volatile components of samples, which is necessary to be discussed for the further study.

### 3.3. HPLC/UHPLC

HPLC/UHPLC is the most frequently used method for Panax species in the qualitative and quantitative analysis. In this review, it is found that stationary phases including C18 column (250 × 4.6 mm, 5 μm) with different brands are used for ginsenosides, OV-170 (500 × 0.25 mm), LiChrosorb for polyacetylenes, polymer C18 column (250 × 4 mm, 10 μm) for trilinoleins, Waters Atlantis HILIC (hydrophilic interaction liquid chromatography) silica (50 × 2.1 mm, 3 μm) [33] for dencichine, and Zorbax SB-Aq column (150 × 4.6 mm, 5 μm) for nucleobases and nucleosides. Moreover, the small particle size ACQUITY UHPLC BEH C18 (2.1 × 100 mm, 1.7 μm) is used in UHPLC. Two-phase solvent systems contain water or buffer solution in water (formic acid, acetic acid, phosphoric acid, ammonium formate, or ammonium acetate) and acetonitrile or methanol. Formic acid in water improves resolution and eliminates peak tailing [34–36]. The solvent range of 1% to 100% is changed to obtain the appropriate gradient elution program. Ginsenosides could be eluted by the solvent range of 30–50% as observed in the literature. UHPLC with less analytical time has the better performance than HPLC.

#### 3.3.1. UV/DAD and ELSD detector

UV detector is the traditional detector for the qualitative and quantitative analysis of chemical compounds in the Panax species (Tables 5 and 6). The detector with its low cost and simple operation has become the most commonly used analytical method in the laboratory. Therefore, it has been widely employed to determine the ginsenosides (malonyl ginsenoside, protopanaxatriol, protopanaxatriol, ocottilol, and oleanane), trilinoleins, polyacetylenes [37], phenolics [38], phytosterols [39], flavonoids, and vitamins [40]. The detection wavelengths for different types of biochemical compounds are various. It is reported that ginsenosides Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, Rh2, Fs, gypenoside XVII, and notoginsenoside Rf could be detected in the wavelength of 203 and 198 nm [41–44]. The detection wavelength is set at 205 nm for trilinoleins [45], 254 nm for polyacetylenes [37], 260 nm for nucleobases and nucleosides [46], and 280 nm for phenolic compounds [38]. However, oleane ginsenosides (ginsenoside Ro) are poor chromatophores with weak UV absorption and are disturbed by solvents (the cut-off wavelength of methanol is 205 nm) that have low sensitivity with UV detection. DAD has the better recognition than conventional UV detection (Table 7). It is widely used to determine polar and non-polar [47], neutral and malonyl ginsenosides [48] in *P. ginseng*, *P. quinquefolius*, and *P. notoginseng*. As a mass detection, ELSD is mainly used for analysis of biological compounds that lack appropriate chromophores (Table 8). It can be used to identify and quantify neutral and acidic ginsenosides Rg1, Rg2, Ro, Rb1, Rb2, Rc, and Rd in *P. ginseng*, while the sensitivity of ELSD is five times lower than that with UV detection [49].

#### 3.3.2. MS detector

Modern analytical techniques based on MS with chromatographic separation have the sensitivity and specificity characteristic when compared with traditional detection analysis of Panax species (Table 9) [10]. Ion sources including atmospheric pressure chemical ionization (APCI) and electrospray ionization (ESI) are used. The APCI can be applied to low molecule and polar compounds, such as 24(R)-pseudoginsenoside F15, ginsenoside Rf, and polyacetylenes [16,50,51]. The most of bioactive constituents of Panax species in the ESI mode has the better performance than that in the APCI mode, especially for the large and moderate polar compounds. Ginsenosides Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, and notoginsenoside Rf have been analyzed with ESI mode in previous studies [52,53]. Dencichine, triterpenoid saponins, nucleobases, nucleosides, and polyacetylenes could be conducted by HPLC-MS as well (Table 10). In addition, MS hyphenations with Q-TOF, IT-TOF, Q-Trap, and Q-Orbitrap have been used to determine ginsenosides accurately and sensitively (Table 11). A total of 234 ginsenosides including 67 potential new ones were isolated tentatively by HPLC–QTOF-MS [54]. It is found that 646 ginsenosides were identified from stems and leaves of *P. ginseng* using linear ion-trap/Orbitrap mass spectrometry [55]. In the qualitative analysis, full
| Method                  | Species               | Part                      | Analytes                                                                 | Reference |
|-------------------------|-----------------------|---------------------------|--------------------------------------------------------------------------|-----------|
| HPLC-DAD                | Panax ginseng         | Root                      | Ginsenosides Rg1, Re, Rf, Rb1, Rc, Rb2, Rd, Re, Rh1, Rf, Rh2, Rg1         | [68]      |
|                         |                       | Root                      | Ginsenosides Rb1, Re, Rg1      | [69]      |
|                         | Panax quinquefolius   | Root                      | Ginsenosides Rg1, Re, Rb1, Rc, Rb2, Rd                                   | [70]      |
|                         |                       | Fresh root                | Ginsenosides and polyacetylenes                                          | [71]      |
|                         | Panax notoginseng     | Root                      | Notoginsenoside R1, ginsenosides Rg1, Re, Rb1, Rd                         | [72]      |
|                         |                       | Root                      | Ginsenosides Rb1, Rc, Rd, Re, Rh1, Rf, Rh2, Rg1, Rg5                    | [73]      |
|                         |                       | Root                      | Ginsenosides Rb1, Rc, Rd, Re, Rh1, Rf, Rh2, Rg1, Rg5, Rg6                | [74]      |
| HSCCC/HPCPC             | Panax ginseng         | Root                      | Ginsenosides Rb1, Re, Rf, Rb1, Rc, Rb2, Rd, Re, Rh1, Rf, Rh2, Rg1         | [75]      |
|                         |                       | Main root, rhizome, fibrous root | Ginsenosides Rb1, Re, Rf, Rb1, Rc, Rb2, Rd, Re, Rh1, Rf, Rh2, Rg1    | [76]      |
|                         |                       | Different parts            | Ginsenosides Rb1, Re, Rf, Rb1, Rc, Rb2, Rd, Re, Rh1, Rf, Rh2, Rg1  | [77]      |
|                         |                       | Flower                    | Ginsenosides Rb1, Re, Rf, Rb1, Rc, Rb2, Rd, Re, Rh1, Rf, Rh2, Rg1  | [78]      |
|                         |                       | Root                      | Ginsenosides Rb1, Re, Rf, Rb1, Rc, Rb2, Rd, Re, Rh1, Rf, Rh2, Rg1  | [79]      |
| Micellar electrokinetic chromatography | Panax ginseng         | Root                      | Ginsenosides Rb1, Re, Rf, Rb1, Rc, Rb2, Rd, Re, Rh1, Rf, Rh2, Rg1         | [80]      |

Table 7: Chemical analysis of Panax species by HPLC-DAD

3.3. Ambient ionization mass spectrometry

Recently, the developed ambient ionization mass spectrometry such as DART-MS and MALDI TOF-MSI are used to evaluate Panax (Table 13) [40,58]. For these methods, direct sampling and ionization are conducted in the open air with no or minimal sample preparation [59]. The most of ginsenosides need derivatization, whereas pseudoginsenoside F11, compound K, protopanaxatriol, and protopanaxadiol are detected without derivatization [59]. In addition, notoginsenoside R1, ginsenosides Rb1, Rg1, and Re from P. ginseng, and P. notoginseng are simultaneously determined by DART-MS [58,60].

3.5. HSCCC/HPCPC

As shown in Table 14, the similar techniques including HSCCC and HPCPC are liquid—liquid partition chromatography. The appropriate solvent systems composed of n-hexane, n-butanol, methylene chloride, methanol, isopropanol, ethyl acetate, and water are employed to isolate the bioactive compounds. In addition, ammonium acetate could reduce the separation time and eliminate emulsification [61]. Ginsenosides Rb1, Re, Rg1, Rd, Re, Rh1, and notoginsenoside R1 could be isolated by HSCCC, and the purity of ginsenosides are more than 95% [62].

3.6. Others

Micellar electrokinetic chromatography could measure the ginsenosides Rg1, Re, Rf, Rb1, Rc, Rb2, Rd, Re, Rh1, Rf, and notoginsenoside R1 in high separation efficiency without any organic solvent and with shorter run time when compared to chromatographic analysis (Table 15) [63]. It can extract dencichine from P. notoginseng with a purity of 98.5% [64]. Moreover, NMR technique in the qualitative analysis is used to discriminate geographical origins of P. ginseng and to obtain the potential markers [65]. It also quantifies malonyl-ginsenosides Re, Rb1, Rb2, Rc, and Rd [66]. HPAE-PAD could analyze amadori compounds in processed ginseng within 15 min of single chromatographic run and eliminate the complex derivatization [67]. Enzyme immunoassay by anti-RF antiserum quantifies ginsenosides Rg2, and RF in P. ginseng [68]. Dencichine is measured by HPAEC for discrimination of P. notoginseng, P. ginseng, and P. quinquefolius [69]. In addition,
Other chemical constituents of Panax species using HPLC-MS

### Table 8

| Method       | Species          | Part       | Analytes                                                                 | Reference  |
|--------------|------------------|------------|--------------------------------------------------------------------------|------------|
| HPLC-ELSD    | P. ginseng       | Root       | Ginsenosides Rg1, Re, Rb1, Rc, Rb2, Rd                                   | [49]       |
| HPLC-ELSD    | Red ginseng      | Root       | Ginsenosides Rg1, Re, Rf, Rg1, Rb1, Rc, Rb2, Rb3, Rd, Rg3, Rk1, Rg2, Rh2 | [77]       |
| HPLC-ELSD    | Black ginseng    | Root       | Less polar ginsenosides                                                  | [78]       |
| HPLC-ELSD    | P. ginseng       | Root       | Ginsenosides Rh1, Rg2, Rg3, Rf, Re, Rd, Rb2, Rc                           | [169]      |
| HPLC-ELSD    | P. quinquefolius | Different parts | Ginsenosides Rg1, Re, Rf, Rh1, Rb1, Rc, Rb2, Rb3, Rd, Rh1              | [104]      |
| HPLC-ELSD    | P. quinquefolius | Different parts | 20(S)-dammarane-3β,12β,20,25-pentol, 25(S)-oocitobol, 20(S)-protopanaxatriol, 20(S)-panaxatriol and 20(R)-dammarane-3β,12β,20,25-tetrol | [105]      |
| HPLC-ELSD    | P. ginseng, P. quinquefolius | Root | Ginsenoside Rf, 24(R)-pseudoginsenoside F11                                 | [90]       |
| HPLC-ELSD    | P. notoginseng   | Root       | Ginsenosides Rg1, Re, Rb1, Rc, Rb2, Rd                                   | [170]      |
| HPLC-ELSD    | P. notoginseng   | Different parts | Ginsenosides Rg1, Re, Rf, Rh1, Rb1, Rc, Rb2, Rd                        | [104]      |
| HPLC-ELSD    | P. notoginseng   | Root       | Ginsenosides Re, Rg1, Rb1, Rb2, Rc, Retoginsenoside R1                   | [52]       |
| HPLC-ELSD    | P. notoginseng, P. ginseng | Root | Notoginsenoside R1, ginsenosides Rg1, Re, Rf, Rg2, Rc, Rb2, Rd, Rg3      | [94,128]  |

### Table 9

| Method       | Species          | Part       | Analytes                                                                 | Reference  |
|--------------|------------------|------------|--------------------------------------------------------------------------|------------|
| HPLC-MS      | P. ginseng       | Root       | Ginsenosides Rb2, Rb1, Rc, Rd, Re, Rf, Rg1, Rg2                           | [118]      |
| HPLC-ESI-MS  | P. ginseng       | Root       | Ginsenosides Rg1, Re, Rb1, Rg1, Rb2, Rd                                  | [18]       |
| HPLC-FD-MS   | P. ginseng       | Ginseng extract | Ginsenosides Rb2, Rb1, Rc, Rd, Re, Rf, Rg1, and Rg2                      | [134]      |
| HPLC-ESI-MS/MS | P. ginseng   | Root       | Ginsenosides Rg1, 20(S)-Rg2, Rb1, Rc, Rb2, malonyl-ginsenoside Rb2 and Rc | [75]       |
| UHPLC-MS     | P. ginseng       | Root       | Low-polar ginsenosides                                                  | [80]       |
| UHPLC-MS     | P. ginseng       | Root       | Ginsenosides Rb2, Rb1, Rg1, Rg2, Rg3, Re, Rd, Re, Rf                       | [171]      |
| HPLC-MS      | P. ginseng       | Root       | Ginsenosides Rg1, Re, Rf, Rb1, Rc, Rb2, Rd, Rg1, Rb2, F1, F2, Fg4, PPT | [122]      |
| HPLC-MS      | P. ginseng       | Fresh root | Ginsenosides Rg1, Re, Rf, Rb1, Rb2, Rd, 20(S)-Rg2, Rc, 20(S)-Rh1, F1, F2, 20(S)-Rg2, 20(S)-protopanaxatriol, compound K, 20(S)-Rh2 | [172]      |
| HPLC-Qtrap-MS| P. ginseng       | Root       | Ginsenosides                                                               | [173]      |
| HPLC-LS      | P. ginseng       | Root       | Notoginsenoside R1, ginsenosides Rb2, Re, Rb1, Rc, Rg1, Rb2, Rd, Rb2, Fg4, Rb2, compound K | [174]      |
| LC/MS/MS     | P. ginseng       | Root       | 15 ginsenosides                                                           | [175]      |
| UHPLC-HRMS   | P. quinquefolius | Root       | Ginsenosides Rb2, Rb1, Rg1, Rc, Rd, Re, Rf, Rg1, Rg2, Rg3, Rb1, Rb2, Ro, F1, F2, Fg4, pseudo ginsenoside F11, notoginsenosides R1, Rg2 | [93]       |
| HPLC-APCI-MS | P. quinquefolius | Root       | 24(R)-pseudoginsenoside F11                                               | [50]       |
| UPLC-MS/MS   | P. ginseng, P. quinquefolius | Different parts | 22 ginsenosides                                                         | [176]      |
| HPLC-MS      | P. ginseng, P. quinquefolius | Root | Ginsenosides Rb2, Rb1, Rc, Ro, Rd, Re, Rf, Rg5, pseudoginsenoside F11    | [88]       |
| UHPLC-ESI-MS | P. notoginseng   | Root       | Ginsenosides Rf, 24(R)-pseudoginsenoside F11                              | [89]       |
| HPLC-MS      | P. notoginseng   | Different parts | Metabolite profiling                                                     | [112]      |
| HPLC-MS      | P. notoginseng   | extraction | Ginsenosides Rg3, Rh1, notoginsenoside R1                                 | [177,178] |
| UHPLC-MS/MS  | P. notoginseng   | Extract    | Notoginsenoside R1, ginsenosides Rg3, Rb1, Re, Rd                         | [120]      |
| UPLC-MS      | P. notoginseng   | Compounds  | Notoginsenoside R1, ginsenosides Rg3, Rd, Rb1, Rf, Rh1, Rb2, Re          | [179]      |
| HPLC-MS      | P. notoginseng   | Root       | Notoginsenoside R1, ginsenosides Rg1, Rb1, Rd, F2, Re                     | [180]      |
| LC-Q-Trap-MS | P. notoginseng   | Extraction | Notoginseng total saponins                                               | [181]      |
| LC-MS/MS     | Steamed notoginseng | Rat plasma | 23 triterpenoids                                                         | [182]      |
| UHPLC-MS     | P. japonicus     | Leaf       | Chikusetsusaponins V, IV, IVa, IV ethyl ester                             | [183]      |
| HPLC-MS      | P. japonicus     | Root       | Notoginsenosides Rg3, Rb1, Rb2, Rb3, Rc, Rd, Re, Rg1, Rg2, 20(S)-Rg2, Rf, | [91]       |
| HPLC-APCI-MS | P. quinquefolius | Root       | Notoginsenosides R1, Rg, Rr and 24(R)-pseudoginsenoside F11              | [51]       |

### Table 10

Other chemical constituents of Panax species using HPLC-MS

| Method       | Species          | Part       | Analytes                                                                 | Reference  |
|--------------|------------------|------------|--------------------------------------------------------------------------|------------|
| HPLC-MS      | Panax            | Root       | Dencichine                                                               | [33]       |
| HPLC-ESI-MS  | P. notoginseng   | Root       | Triterpenoid saponins                                                    | [184]      |
| HPLC-MS      | P. notoginseng   | Root       | Nucleohases, nucleosides, and saponins                                    | [46]       |
| NanoESI-MS   | P. ginseng       | Root       | Polyoctetylenes                                                          | [185]      |
| UPLC-MS/MS   | P. quinquefolius | Root       | Lipidomics                                                               | [185]      |
| LC-Q-TOF-MS  | P. ginseng       | Root       | Malonyl ginsenoside, amino acids, polysaccharides                         | [187]      |

### 4. Analytical methods applied to Panax species

As we all know, the different processing methods, species, parts, regions, and ages have different chemical information. To display the chemical markers of different conditions, we have reviewed the advanced techniques evaluating samples of Panax. In addition, the
| Method                          | Species                  | Part                          | Analytes                                                                 | Reference |
|--------------------------------|--------------------------|-------------------------------|--------------------------------------------------------------------------|-----------|
| HPLC-ESI-MS/MS                 | *P. ginseng*             | Root                          | Multicomponent quantification fingerprint                                | [188]     |
| UHPLC-QTOF-MS                  | *P. ginseng*             | Different parts               | Qualitative analysis                                                     | [189]     |
| LC-QTOF/MS                     | *P. ginseng*             | Root                          | Fingerprint analysis                                                    | [190]     |
| LC-QTOF/MS/MS                  | *P. ginseng*             | Root                          | Ginsenosides Rc, Rb2, Rb3, malonyl-ginsenosides                          | [191]     |
| UHPLC-QTOF-MS                  | *P. ginseng*             | Root                          | Metabolomics analysis                                                   | [116]     |
| UHPLC-QTOF-MS                  | *P. ginseng*             | Hairy root                    | Metabolomics analysis                                                   | [35]      |
| LC-QTOF/MS                     | *P. ginseng*             | Root                          | Metabolite profiling                                                    | [121]     |
| UPLC-QTOF/MS                   | *P. ginseng*             | Ginseng extract               | 22 ginsenosides                                                         | [6]       |
| UHPLC-Q-TOF MS                 | *P. ginseng*             | Root                          | Metabolomics analysis                                                   | [194]     |
| UPLC-QTOF/MS                   | *P. ginseng*             | Root                          | Metabolite profiling                                                    | [195]     |
| UPLC-QTOF-MS                   | *P. ginseng*             | Different parts               | 58 ginsenosides                                                         | [201]     |
| UHPLC-QTOF-MS                  | *P. ginseng*             | Root                          | Cell-based neuroactivity screening                                       | [202]     |
| UHPLC-QTOF-MS                  | *P. ginseng*             | Root                          | Transformation of ginsenosides                                           | [203]     |
| UHPLC-QTOF-MS                  | *P. ginseng* (different processed) | Root                          | Metabolite profiling                                                    | [204]     |
| UHPLC-QTOF-MS                  | *P. ginseng* (different age) | Root                          | Metabolite profiling                                                    | [205]     |
| UHPLC-QTOF-MS                  | *P. quinquefolius*       | Root                          | Fingerprint analysis                                                    | [206]     |
| LC-TOF-MS                      | *P. quinquefolius*       | Root                          | Metabolomics analysis                                                   | [207]     |
| UPLC-QTOF/MS                   | *P. quinquefolius*       | Root                          | Metabolomics analysis                                                   | [209]     |
| LC-MS                          | *P. quinquefolius*       | Root                          | Fingerprint analysis                                                    | [210]     |
| HPLC-ESI-MS                    | *P. quinquefolius*       | Root                          | Metabolomics analysis                                                   | [211]     |
| HPLC-MS*                       | *P. quinquefolius*       | Root                          | 59 ginsenosides of protopanaxadiol, protopanaxatriol, oleane and ocottillo types | [81]     |
| UHPLC-QTOF-MS/MS               | *P. notoginseng*         | Root                          | Metabolite profiling                                                    | [74]      |
| UHPLC-QTOF-MS                  | *P. ginseng, *P. quinquefolius* | Leaf                          | Metabolomics analysis                                                   | [36]      |
| HPLC-ESI-MS                    | *P. ginseng*             | Root                          | Metabolite profiling                                                    | [99]      |
| HPLC-ESI-MS                    | *P. notoginseng*         | Different parts               | Metabolomics analysis                                                   | [113]     |
| LC-MS                          | *P. notoginseng*         | Root                          | Metabolite profiling                                                    | [15]      |
| UHPLC-QTOF-MS                  | *P. notoginseng*         | Root                          | Metabolite profiling                                                    | [53]      |
| UHPLC-QTOF-MS                  | *P. notoginseng*         | Root                          | Metabolite profiling                                                    | [72]      |
| LC-QTOF/MS                     | *P. notoginseng*         | Extract                       | Metabolomics analysis                                                   | [212]     |
| LC-QTOF/MS                     | *P. notoginseng*         | Leaf                          | Metabolite profiling                                                    | [34]      |
| UHPLC-ESI-MS and UHPLC-QTOF-MS | *P. notoginseng*         | Flower bud                    | Metabolite profiling                                                    | [70]      |
| UHPLC-ESI-MS                   | *P. notoginseng*         | Root                          | Fingerprint analysis                                                    | [213]     |
| HPLC-QTOF-MS                   | *P. notoginseng*         | Root                          | Metabolite profiling                                                    | [54]      |
| LC-triple-TOF/MS               | *P. notoginseng*         | Extraction                    | Ginsenosides Rb2, Rb3, Re, Rf, Rg1, and notoginsenoside R1              | [214]     |
| UPLC/Q-TOF/MS                  | *P. notoginseng*         | Leaf                          | Ginsenosides Rb2, Rb3, notoginsenosides Fe, Fe2                           | [215]     |
| HPLC-QTOF/MS                   | *P. ginseng, *P. notoginseng, *P. japonicus, *P. quinquefolius* | Root                          | Metabolite profiling                                                    | [88]      |
| LC-MS-IT-QTOF                  | *P. ginseng, *P. quinquefolius, *P. notoginseng* | Root                          | Qualitative analysis                                                   | [87]      |
| UHPLC-IMC-NLF                  | *P. ginseng, *P. quinquefolius, *P. notoginseng* | Root                          | Malonyl-ginsenosides                                                   | [216]     |
| UPLC-LTQ-Qbittrap-MS           | *P. ginseng, *P. quinquefolius, *P. notoginseng* | Different parts               | Malonyl-ginsenosides                                                   | [217]     |
| UHPLC-QE-HRMS                  | *P. ginseng, *P. quinquefolius, *P. notoginseng* | Root                          | 101 compounds                                                          | [135]     |
mechanisms of chemical compounds changing for Panax are illustrated.

4.1. Raw and processed ginseng

Processing Panax species leads to various bioactive characteristics, which have been used in the treatment of different diseases when compared to raw ginseng. In the Chinese medicine, “Sheng Da Shu Bu” and “Sheng Leng Shu Wen” with regard to raw P. notoginseng are used for hemostasis and cardiovascular diseases, whereas the steamed form is used to “nourish” blood [10]. Those theories suggested that raw and processing have the opposite effect on some illness. Different chemical profiles in the processing have been investigated in the previous study. As a formal method, from

| Method | Species | Part | Analytes | Reference |
|--------|---------|------|----------|-----------|
| 2D LC/LTQ-Orbitrap-MS/NMR | P. ginseng | Stems and leaves | A total of 646 ginsenosides were characterized, and 427 have not been isolated from the genus of Panax L. | [55] |
| 2D LC-ESI | P. ginseng | Extraction | Triterpenoid saponins | [218] |
| 2DLC-MS | P. ginseng | Extraction | Ginsenosides Rd, Re, Rb1, Rb2, Rd | [219] |
| 2D chromatographic method | P. notoginseng | Root | Ginsenosides Rb2, Rg1, Rg2, Rh1, Rh2, Rd, 20(S)-Rg3, notoginsenosides R1, Ts | [57] |
| HILIC × RPLC | P. notoginseng | Root | Metabolomics analysis | [56] |
| 2D LC-QTOF-MS | P. notoginseng | Extraction | Total saponins | [220] |

| Method | Species | Part | Analytes | Reference |
|--------|---------|------|----------|-----------|
| 2D LCQ-TOF-MS | P. ginseng | Stems and leaves | A total of 646 ginsenosides were characterized, and 427 have not been isolated from the genus of Panax L. | [55] |
| 2D LC-ESI | P. ginseng | Extraction | Triterpenoid saponins | [218] |
| 2DLC-MS | P. ginseng | Extraction | Ginsenosides Rd, Re, Rb1, Rb2, Rd | [219] |
| 2D chromatographic method | P. notoginseng | Root | Ginsenosides Rb2, Rg1, Rg2, Rh1, Rh2, Rd, 20(S)-Rg3, notoginsenosides R1, Ts | [57] |
| HILIC × RPLC | P. notoginseng | Root | Metabolomics analysis | [56] |
| 2D LC-QTOF-MS | P. notoginseng | Extraction | Total saponins | [220] |
| Method                  | Species       | Part           | Analytes                                                                 | Reference |
|-------------------------|---------------|----------------|--------------------------------------------------------------------------|-----------|
| HPLC-UV, UHPLC-PDA, CE-UV, IR | *P. notoginseng* | Main root, rhizome | Fingerprint analysis                                                      | [71]      |
| HPLC-UV, GC-MS          | *P. ginseng*  | Root           | Ginsenosides Rg1, Re, Rf, Rb1, Rg2, Rb1, Rb2, Rg3, F2, compound K, Rk1, Rg5, Rh2 | [20]      |
| HPLC-UV, HPLC-MS        | *P. notoginseng* | Extract         | Fingerprinting and quantitative analysis                                  | [234]     |
| HPLC-DAD, LC-ESI-MSn    | *P. notoginseng* | Leaf           | Ginsenosides Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, Rg2                           | [235]     |
| GC–MS, LC–MS            | *P. ginseng*, *P. quinquefolius* | Different parts | Chemical profiles and anticancer                                         | [236]     |
| LC-ELSD, LC-Q-TOF-MS    | *P. vietnamensis* | Radix and rhizome | Ginsenosides Rg1, Re, Rb1, Rc, Rb2, Rg1, majonoside R1, R2 and vina-ginsenoside R2 | [96]      |

**Scheme 1.** The potential transformation pathway of protopanaxadiol ginsenosides after processing.
raw to processed material steaming with different temperatures and times has been used. *P. ginseng* is steamed at 98°C and 120°C at 2 h, 6 h, and 9 h, which shows the various bioactive constituents. Time-dependent profiling of raw and steamed *Panax* species is studied [72–74]. “Red ginseng” is formed at two- or three-time steaming and “black ginseng” is formed with cyclic nine-time steaming at 98°C for 3 h. Therefore, phytochemical components including saponins and volatile oils are reviewed in this
investigation. It is found that chemical constituents with polar ginsenosides can be transformed to low polar ginsenosides by hydrolisi, isomerization, and dehydration [75]. The concentration of polar ginsenosides, notoginsenoside R1, ginsenosides Rg1, Re, Rb1, Rc, Rb2, Rb3, and Rd, decreased by steaming, whereas that of low polar ginsenosides, Rh1, Rg2, Rg3, Rh2, Rg5, and Rs4, increased, and ginsenosides Rg3, Rg5, and Rk1 are the unique compounds from steamed ginseng [44, 76–80].

Usually, the types of saponins in the *Panax* species are mainly protopanaxadiol, protopanaxatriol, ocatillol, and oleanane. As shown in Scheme 1, protopanaxadiol including ginsenosides Rb1, Rb2, Rb3, and Rc converted to Rd by hydrolysis of a glycosylation moiety at C-20. Then, the loss of glycosylation moiety at C-20 and C-3 of Rd through hydrolysis generated ginsenosides 20(R/S)-Rg3 and 20(R/S)-Rh2, Rk1, and Rg5 under the reaction conditions gradually increased [44, 74, 75, 77–81]. Interestingly, ginsenosides Rk2 and Rg3 were deduced to 20(R/S)-Rg3 by Δ20(21) and Δ20(22) dehydration at C-20. Ginsenosides Rk1 and Rg5 are hydrolyzed to generate Rk2 and Rh3 by loss of a glycosylation moiety at C-20 [74, 75, 80, 81]. Protopanaxatriol including ginsenosides Re and Rg1 produced 20(R/S)-Rg2, F1, Rg6, 20(R/S)-Rh1, and Rg4 through hydrolysis of a glycosylation moiety at C-20 and C-6 when the creaming with high-temperature and long-time shown in Scheme 2 [74, 75, 77, 80, 81]. Specifically, ginsenosides 20(R/S)-Rf2 was deduced by C-24 and C-25 hydration of Rg5 [81]. In addition, malonyl and acetyl ginsenosides could convert to the corresponding neutral ginsenosides through demalonylation and deacetylation reaction shown in Scheme 3 [74, 75]. Such as acetyl-ginsenosides 20(R/S)-Rs3, Rs4, and Rs5 were deduced to be generated from malonyl-ginsenosides Rb1, Rb2, and Rc through hydrolysis, decarboxylation, and dehydration [74, 75]. For oleanane type, the chemical transformations have not been studied up to now. The possible transformation pathways deduced are shown in Scheme 4 [81].

4.2. Different species

Different species of *Panax* have different effects on diseases. *P. ginseng* is used for its anticancer effect [82]. While *P. quinquefolius* has a good performance on antidiabetic, anti-inflammatory, and neuroprotective effects [83–85]. *P. notoginseng* always have effects on the cardiovascular system, hemostatic, and antioxidant activities [86]. *P. japonicus*, *P. vietnamensis*, *P. stipuleanatus*, *P. sokpayensis*, and *P. bipinnatifidus* are also used to protect and treat diseases all over the world. Usually, ginsenosides are the main bioactive components for the *Panax* species. Yao et al have reported that 623 ginsenosides in the ethanol extract of *P. ginseng*, *P. quinquefolius*, and *P. notoginseng* are discovered, and among those, 437 are potentially novel ginsenosides [87]. Polysaccharides, essential oils, phenolic acids, alkaloids, and others were also investigated in a previous study [3]. The similar morphological characteristics especially medicinal power and its extraction are hard to evaluate them in the markets. The fake and inferior goods may arise owing to price difference for *Panax* species largely. It is therefore necessary to select some quality markers for distinguishing *Panax*.

For saponins, ginsenoside Rf is only detected in *P. ginseng*, whereas 24(R)-pseudoginsenoside F11 is mainly detected in *P. quinquefolius* [88–90]. Ginsenoside Rs1 is used to differentiate *P. ginseng* and *P. quinquefolius* also [91]. Furthermore, the higher amount of Rg1 group (Rf, Rg1) is in *P. ginseng* and that of the Rb group is in the *P. quinquefolius* [92]. A higher protopanaxadiol/protopanaxatriol ratio for *P. quinquefolius* is about 3, while the value is between 1 and 3 for *P. ginseng* [93]. When *P. notoginseng* and *P. quinquefolius* are compared, the former has the highest
ginsenoside content (9.176%), and the latter has the highest poly-acetylene content (0.08%) [37]. Notoginsenoside R1 is detected in both P. notoginseng and P. ginseng [51], whereas ginsenoside Rg3 is observed in the red ginseng [94]. Ginsenoside Rc was not detected in P. sokpayensis, and ginsenosides Rf, Rc, and Rb2 are not detected in P. bipinnatifidus [95]. P. vietnamensis mainly has ooctillol type of ginsenosides [96]. To describe the more chemical information, metabolic components combined with multivariate statistical analysis, hierarchical clustering analysis, principal component analysis, and partial least squares discriminant analysis have been applied to evaluate different species and to select the appropriate chemomarkers [97]. The results indicated that ginsenoside Rf, 20(S)-pseudoginsenoside F11, malonyl-ginsenoside Rb1, and ginsenoside Rb2 could be used to differentiate P. ginseng, P. notoginseng, P. japonicus, and P. quinquefolius [98]. 24(R)-Pseudoginsenoside F11, ginsenoside Rf, Ra1, F2, and 20-glucoginsenoside Rf can differentiate processed P. ginseng and P. quinquefolius [99]. The metabolic constituents of leaves to avoid damaging the roots can separate Panax species [100]. Pseudoginsenoside F11, Rb3, malonyl-notoginsenoside Fd, malonyl-ginsenosides F3, Rb3, Re, F3, R2, and F1 are selected as the chemical markers for leaves of P. ginseng and P. quinquefolius [36]. For essential oil, hexanal, 2-pyrrolidnone, (E)-2-heptenal, (E)-2-octenal, heptanal, isospathulenol, (E, E)-2,4-decadienal, 3-ocoten-2-one, benzaldehyde, 2-pentylfuran, and (E)-2-nonenal can discriminate P. ginseng and P. notoginseng [29]. Mono- and oligo-saccharide are similar in the different regions and Panax species [25]. However, dencichine varied in Panax species, the highest (0.36 ± 0.02%) is in P. notoginseng, then P. ginseng (0.31 ± 0.06%) and P. quinquefolium (0.1 ± 0.01%), and the lowest (0.03 ± 0.07%) was in steamed P. ginseng. The contents of panaxfuraynes A and B are less than 3 and 2 ng/g in the roots of P. quinquefolius, P. japonicum, P. notoginseng, and P. ginseng, whereas they were not found in P. japonicum [101].

4.3. Different parts

Different parts include aerial parts (flower, leaf, and stem) and underground parts (rhizome, main root, lateral root, and root hair) in Panax species, which have been used for medicinal purposes. As a medicinal tea, flower and leaf are used to prevent disease for the human in the eastern world, especially in China. An official herbal medicine, leaf of P. ginseng is recorded in Chinese Pharmacopoeia. Different parts of Panax species have long been used. For instance, rhizomes of P. notoginseng and P. ginseng are called as “Jinkou” and “Lutou” in the traditional medicine, respectively. Different parts have various pharmacological activities [86]. The chemical profile for different parts of Panax species is significant.

In P. ginseng, the content of ginsenosides is higher in the leaf and root hair and lower in stem and other parts. The content of ginsenosides in the root and root hair increases with age from one to five years [102]. More kinds of ginsenosides are found in cork than those in cortex, phloem, xylem, and resin canals; the content of ginsenosides of phloem, xylem, and resin canals from branch root is high than that from main root [103]. The content of total phenols in fruit and leaf is higher than in roots, including major phenolic compounds chlorogenic acid, gentisic acid, p- and m-coumaric acid, and rutin

Scheme 4. The potential transformation pathway of oleanane ginsenosides after processing.
Moreover, the order for triacylglycerol content is rhizome > main root > root hair. Ginsenosides in *P. quinquefolius* follow this order leaf > root hair > rhizome > stem [104]. Sapogenins are found more in stem and leaves than other parts of *P. quinquefolius* [105]. Both *P. ginseng* and *P. quinquefolius* mainly have ginsenosides Rg1, Re, and Rb2 for leaves, and ginsenosides Re, Rb1, and Rc for root hair [41]. The reason for ginsenosides accumulation in *P. ginseng* main root and *P. quinquefolius* lateral roots may be higher rates of C assimilation to C accumulation [106]. In *P. notoginseng*, different parts can be identified based on saponin content difference [107]. The type of 20(S)-protopanaxatriol is mainly distributed in the underground parts, whereas 20(S)-protopanaxadiol is mainly distributed in the aerial parts [108,109]. Different parts could be identified by metabolomic combined with principal component analysis [71,110,111]. Notoginsenosides R2, Fa, Q, S, Fc, R1, H, A, B, ginsenosides Rb1, Rb2, Rb3, Rc, Rd, F2, Rb2, Rg1, Re, Rf, Rg2, malonyl-ginsenoside-Rb1, and 20-O-glucoginsenoside-RF contribute to up-or down-regulation of different parts of *P. notoginseng* [112]. The main roots have 31% higher ginsenosides content than rhizome [96].

### 4.4. Different region and age

*P. ginseng* is mainly distributed in Korea, North Korea, and Northeastern China, *P. quinquefolius* in America and Canada, and *P. notoginseng* in Southwestern China. Geographical origin is a major influential factor for quality control [35]. Metabolomics combined with OPLS-DA could be used to discriminate *P. ginseng* of different regions [65]. The contents of 1,2-dilinoleoyl-3-oleoyl-glycerol of *P. ginseng* from Korea, Japan, and China are 0.41 ± 0.009 mg/g, 0.45 ± 0.01 mg/g, and 0.22 ± 0.008 mg/g, and those of trilinolein are 0.37 ± 0.009 mg/g, 0.39 ± 0.016 mg/g, and 0.27 ± 0.009 mg/g. Furthermore, *P. quinquefolius* roots cultivated in Jilin Province are similar to those cultivated in China in the compositions [113], whereas those grown in China and North America showed no major difference [93]. Ginsenosides Rb1, Rc, Rb2, Rg1, and Rd are influenced by location [114]. The highest polyacetylene content is distributed in Nagano, Japan [37]. Chemical constituents of rhizome and main roots of *P. notoginseng* from Wenshan, Honghe, and Kunming have no significant difference [115]. Different growing years may lead to different chemical profiles. For *P. ginseng*, seven ginsenosides show age-dependent variations [116]. Metabolites combining with multivariate statistical methods could classify different ages, especially for 4, 5, and 6 years [117]. The total contents of ginsenosides for main root and fibrous root in four years are highest [118]. The highest concentrations of stigmastanol and β-sitosterol are found in 6-year-old *P. ginseng* cultivated in Jinan, Korea [39]. For notoginseng, different growth years can be identified by the saponin content, the content of most and total saponins in the order is 3 > 2 > 1-year-old in the main root samples [107]. The best season for harvesting is September to October [13].

### 4.5. Biochemical analysis

Metabolism of *Panax* species in the different tissues could obtain a better understanding of biological effects. Ginsenosides Rg1, Rb1, and Rd of *P. notoginseng* in rat tissues (kidney, liver, heart, spleen, and lung) are determined. The highest concentrations of three saponins were at 90 min except for spleen after oral dose, whereas after intravenous administration, they could not detect in all tissues after 8 h [119]. After nasal administration, notoginsenoside Rb1, ginsenosides Rg1, Rb1, Rd, and Re from *P. notoginseng* have been determined in brain [120]. The metabolites in the urine after being administered orally ginseng decoction were used to distinguish normal control group, deficiency of vital energy model group, and ginseng treatment group and to find potential biomarkers [121].

Biotransformation of *P. ginseng* in the rat intestinal microflora indicated that protopanaxadiol-type ginsenosides were more easily metabolized than protopanaxatriol-type ginsenosides [122].

### 5. Conclusion

In this review, different sample preparations including Soxhlet extraction, heat reflux extraction, ultrasonic extraction, solid phase extraction, microwave-assisted extraction, pressurized liquid extraction, enzyme-assisted extraction, accelerated solvent extraction, matrix solid phase dispersion extraction, and pulsed electric field were compared. The TLC technique has been used to quantify and identify *Panax* species quickly, although it always needs standards and lacks uniqueness for bioactive compounds. GC–MS could be used to determine ginsenosides, phenolic acids, dencichine, pesticide residues, and volatile components, although for some non-volatile components complex operation is required. UHPLC with less analytical time has the better performance than HPLC, and DAD has the better recognition than conventional UV detection. HPLC tandem MS has the sensitivity and specificity characteristic when compared with traditional detection. In the liquid–liquid partition chromatography (HSCCC and HPCPC), ammonium acetate could reduce the separation time and eliminate emulsification. After processing ginseng, chemical constituents with polar ginsenosides can be transformed to low polar ginsenosides by hydrolysis, isomerization, and dehydration. Ginsenoside RF is only detected in *P. ginseng*, whereas 24(R)-pseudo-ginsenoside F13 is mainly detected in *P. quinquefolius*. When *P. notoginseng* and *P. quinquefolius* are compared, the former has the highest ginsenoside content (9.176%) and the latter has the highest polyacetylene content (0.08%). The content of ginsenosides in the leaf and root hair is higher, and it is lower in stem and other parts of *P. ginseng*. In addition, the content of total phenols in fruit and leaf is higher than in roots. For *P. notoginseng*, the type of 20(S)-protopanaxatriol is mainly distributed in the underground parts, whereas 20(S)-protopanaxadiol is mainly distributed in the aerial parts. *P. ginseng* is mainly distributed in Korea, North Korea, and Northeastern China, *P. quinquefolius* in America and Canada, and *P. notoginseng* in Southwestern China. Protopanaxadiol-type ginsenosides were more easily metabolized than protopanaxatriol-type ginsenosides in the rat intestinal microflora.

From the current review, the present analysis of *Panax* species is not sufficient. The following aspects need to be investigated.

1. According to previous studies, the different sample preparations and analytical methods have been used to evaluate ginsenosides of *Panax* species. It is necessary that the harmonious and practical standard criteria method is established for determining ginsenosides of different species, parts, and ages quickly and accurately.

2. As we all know, ginseng has been widely used for prevention and treatment of diseases all over the world. Meanwhile, the criteria of Chinese Pharmacopoeia, United States Pharmacopeia, Japanese Pharmacopoeia, and South Korean Pharmacopoeia for *P. ginseng* have been developed. Different countries have different criteria. It is expected that the uniform criteria for ginseng should be established for development of the ginseng industry.

3. As an oleanane type, ginsenoside Ro was only detected in the *P. ginseng* and *P. quinquefolius*, which could be used to inhibit testosterone 5α-reductase and for testosterone-treated disease [123]. Both Ro and its transformation products in red ginseng are the bioactive constituents [124]. The chemical transformation pathway and the metabolism in vitro and in vivo are the key research in the further investigation. Furthermore, in
Conflicts of interest

All authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgr.2019.12.009.

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