

Review

# Advances in Saponin Diversity of *Panax ginseng*

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**Abstract:** Ginsenosides are the major bioactive constituents of *Panax ginseng*, which have pharmacological effects. Although there are several reviews in regards to ginsenosides, new ginsenosides have been detected continually in recent years. This review updates the ginsenoside list from *P. ginseng* to 170 by the end of 2019, and aims to highlight the diversity of ginsenosides in multiple dimensions, including chemical structure, tissue spatial distribution, time, and isomeride. Protopanaxadiol, protopanaxatriol and C17 side-chain varied (C17SCV) manners are the major types of ginsenosides, and the constitute of ginsenosides varied significantly among different parts. Only 16 ginsenosides commonly exist in all parts of a ginseng plant. Protopanaxadiol-type ginsenoside is dominant in root, rhizome, leaf, stem, and fruit, whereas malonyl- and C17SCV-type ginsenosides occupy a greater proportion in the flower and flower bud compared with other parts. In respects of isomeride, there are 69 molecular formulas corresponding to 170 ginsenosides, and the median of isomers is 2. This is the first review on diversity of ginsenosides, providing information for reasonable utilization of whole ginseng plant, and the perspective on studying the physiological functions of ginsenoside for the ginseng plant itself is also proposed.

**Keywords:** ginsenoside; *Panax ginseng*; chemical structure; tissue spatial distribution

## 1. Introduction

*Panax ginseng* Meyer (*P. ginseng*), known as the king of all herbs, has been frequently used as traditional medicine and healthy food in China, Korea, and Japan. In 2012, *P. ginseng* was approved as a new food resource by Chinese government, and it has been widely used as the raw material of healthcare products [1]. Ginseng contains a large amount and number of ginsenosides. More than 289 saponins were reported from eleven different *Panax* species [2]. In addition, at least 123 ginsenosides have been identified in different *P. ginseng* species, and these include both naturally occurring compounds and those from steaming and biotransformation [3]. In addition, 112 saponins were reported from raw or processed ginseng, including hydrolysates, semisynthetic, and metabolites [4]. Ginsenosides are known to possess a lot of biological activities including regulatory effects on immunomodulation, protection functions in the central nervous and cardiovascular systems, anti-diabetic, anti-aging, anti-carcinogenic, anti-fatigue, anti-pyretic, anti-stress, boosting physical vitality, and promotion of DNA, RNA, and protein synthesis activities [5–9]. In addition, the biosynthesis of triterpenoid is an important factor of saponin diversity. Consequently, biosynthetic mechanisms

for the backbone synthesis [4] and structural diversification and genes/enzymes involved in the biosynthesis [10] were reviewed in the cited references. Therefore, ginsenosides are recognized as the main bioactive components and a key index for quality evaluation of ginseng.

Due to the complexity of the ginsenosides and their structures, multi-platform analytical techniques are used in the detection of ginseng products, such as thin layer chromatography (TLC), high performance thin layer chromatography (HPTLC), gas chromatography (GC), high performance liquid chromatography (HPLC), ultra performance liquid chromatography (UPLC) [3,11,12]. However, these methods detect only small numbers of ginsenosides and lack in provision of structural information. Liquid chromatography coupled with tandem mass spectrometry can provide structural information with high sensitivity, specificity, and versatility in characterizing complex natural product samples. It has been successfully used as a powerful tool for ginsenoside analysis with high throughput [1]. In recent years, a number of novel ginsenosides have been detected in aerial parts of the ginseng plant using the HPLC-MS/MS method, such as stems, leaves, rhizomes, flowers, and flower buds, which enlarged the number of ginsenoside family members [13–15]. Several reviews have summarized the progress from a viewpoint of structural features, and conclude that ginsenosides are generally classified into four groups: protopanaxadiol type (PPD), protopanaxatriol type (PPT), C17 side-chain varied type (C17SCV), and oleanolic acid type (OA) [2,16–18]. However, spatial distribution of ginsenoside in different parts of *P. ginseng* is not yet summarized. This information will make better use of the whole ginseng plant and provide clues for studying the biological function of saponins. This review updates the ginsenoside list (from *P. ginseng*) to 170 by the end of 2019, and aims to highlight the diversity of ginsenosides in multiple dimensions, including chemical structure, tissue spatial distribution, time, and isomeride.

## 2. History of Saponins Isolated from *P. ginseng*

The history of ginsenoside isolation can be divided into three periods (before 1980 for Period I, 1980–2000 for Period II, after 2000 for Period III) based on the development of analytical techniques. The study on ginsenoside started in 1854. A ginsenoside-containing constituent was firstly isolated from American ginseng by American scholar Garriques [19], and subsequently, Japanese chemists reported panaquilon, panacon, panaxasapogenol, and ginsenin preliminarily separated from *P. ginseng*. For almost 100 years since the middle of the nineteenth century, it was difficult to obtain a pure ginsenoside due to the under development of separation techniques. In the early 1950s, with the development of separation technology and the invention of modern analytical instruments, such as GC, TLC, etc., the studies on the chemical ingredient of ginseng made remarkable progress. In 1963, for the first time, Shibata et al. reported the chemical property and structure of the panaxadiol separated from ginseng root [20]. In the 1970s, 17 ginsenosides were detected in ginseng, named as ginsenoside Ro, Ra, Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, Rg2, Rg3, F1, F2, F3, Rb3, Rh, and 20-glucoginsenoside-Rf [21–26]. The second period began when the  $^{13}\text{C}$  NMR technique was introduced into the structure analysis of ginsenosides. By comparison of the measured  $^{13}\text{C}$  NMR spectroscopic data with known compounds, the accurate structure of new ginsenosides (G-Rh1, Rh2, Rh3, Rg4, Ra1, Ra2, Ra3, La, Rf2, Rs3, Ia, Ib, etc.) could be resolved from different parts of ginseng (root, steamed root, flower bud, stem, and leaf). In this period, more and more scientists focused on ginsenoside isolation, and most of ginsenosides were found in the aerial parts of ginseng [27–36]. The third period was defined by high-efficiency separation methods, as methods such as high-speed counter current chromatography (HSCCC), high performance centrifugal partition chromatography (HPCPC), and 2D NMR spectroscopic techniques were used for separating and identifying ginsenosides. The application of these powerful new techniques helps to identify the complex chemical structure, for instance, C17 side-chain variation and malonyl group. More than 50 new ginsenosides were isolated from 2000 to 2019, among which most of those possessed variations in the C17 side-chain, besides a part of malonyl ginsenosides [37–41].

### 3. Classification of Saponins Identified from *P. ginseng*

Although most ginsenosides have a rigid four-trans-ring steroid skeleton, they produce multiple pharmacological and biological effects that are different from one another due to minor variations on: (1) Type of sapogenins; (2) number, type, and site of glycosyl units; and (3) modification of C17 side-chains [11,42,43]. Therefore, the study of ginsenoside structure will help to elucidate the mechanism of multiple functions of ginsenosides. The reported ginsenosides are classified into protopanaxadiol type (PPD), protopanaxatriol type (PPT), oleanolic acid type (OA), and C17 side-chain varied (C17SCV) subtypes according to their determined sapogenin structures (Figure 1). The glycosyl components of saponin were mainly  $\beta$ -D-glucopyranosyl group, followed by  $\alpha$ -L-rhamnopyranosyl group, a few binding  $\alpha$ -L-arabinopyranosyl group and  $\beta$ -D-xylopyranosyl group, and the  $\beta$ -D-glucopyranosiduronyl group only appears in saponins with oleanolic acid-type (OA) sapogenin. In dammarane-type triterpenoid saponins,  $\beta$ -D-glucopyranosyl group (2 $\rightarrow$ 1)- $\beta$ -D-glucopyranosyl oligosaccharide chains occur more frequently, and are mostly bound to C-3 of sapogenin to generate oxyglycoside;  $\beta$ -D-glucopyranosyl group (2 $\rightarrow$ 1) $\rightarrow$  $\alpha$ -L-rhamnopyranosyl group oligosaccharide chains are mostly bound to C-6 of sapogenin to form oxyglycoside. The tetracyclic parent nucleuses are relatively stable, whether they are PPT and/or PPD type. Moreover, the substituents that occur in the C17 side-chains often undergo oxidation, reduction, cyclization, and epimerization, contributing to diversity in chemical structure [12,16]. Table 1 displays the molecular formulas, molecular masses, and structural categories of 170 ginsenosides, isolated from different parts of *P. ginseng*. As a result, four ginsenosides are OA type, 59 ginsenosides are PPD type, 42 ginsenosides are PPT type, and 65 ginsenosides are C17CSV type. Among them, four PPD-type ginsenosides (Rb1, Rb2, Rc, Rd), three PPT-type ginsenosides (Re, Rf, Rg1), and one OA-type ginsenoside Ro (the structures are shown in Figure 2) are the most abundant in *P. ginseng*, and account for more than 70% of the total saponins [5].

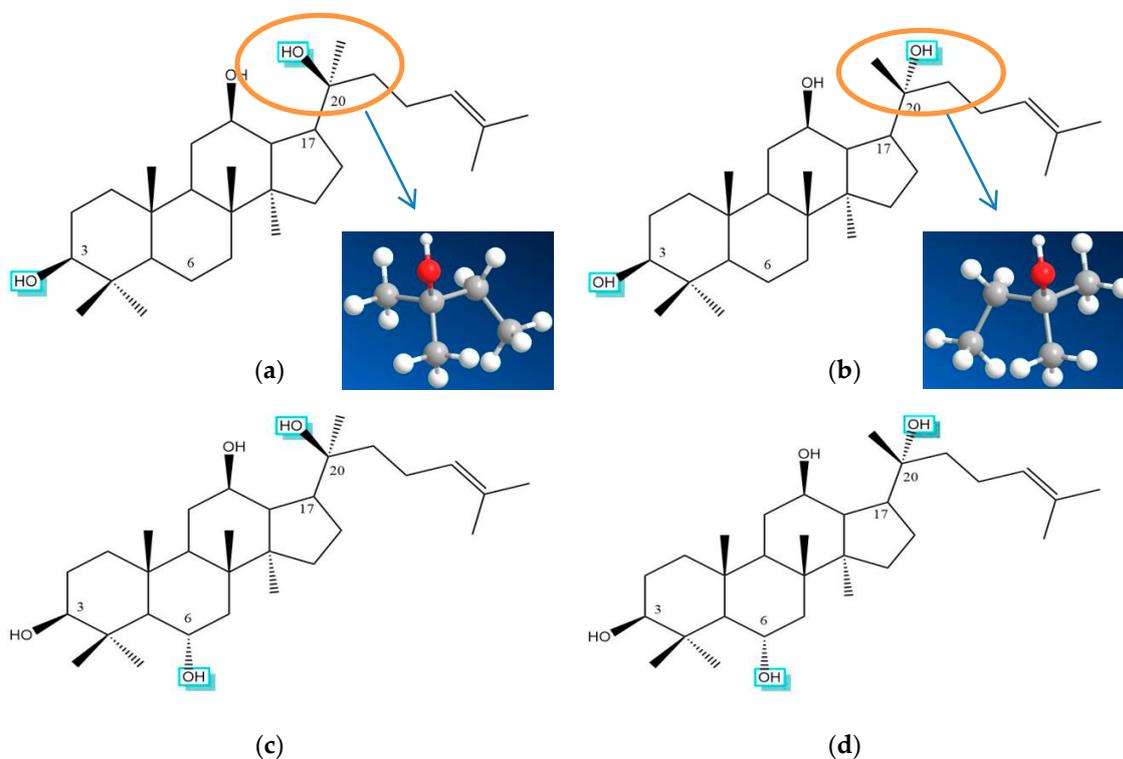
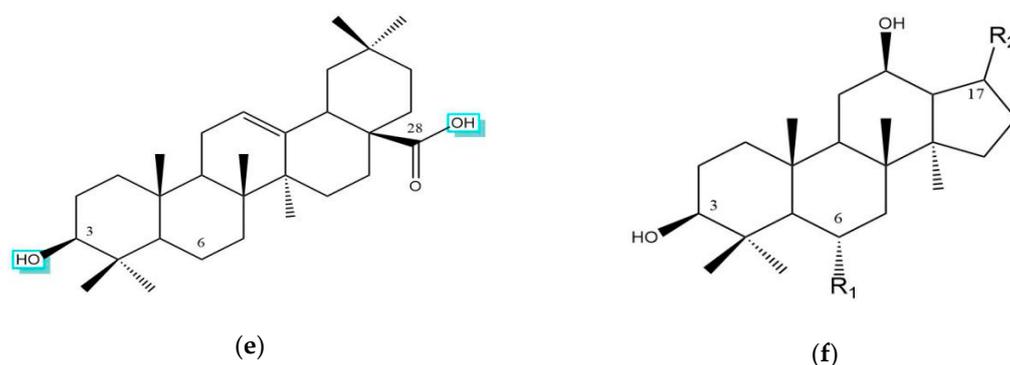


Figure 1. Cont.



**Figure 1.** Structures of PPD, PPT, OA, and C17SCV sapogenins. The typical glycosylation sites for these sapogenins are marked in blue frame. (a) 20(S)-PPD: Protopanaxadiol type; (b) 20(R)-PPD: Protopanaxadiol type; (c) 20(S)-PPT: Protopanaxatriol type; (d) 20(R)-PPT: Protopanaxatriol type; (e) OA: Oleanolic acid type; (f) C17SCV: C17 side-chain variation type. R1 in C17SCV: -H, -OH, -OR. R2 in C17SCV: The variations in the C17 side-chain mainly comprise H<sub>2</sub>O-addition, hydroxylation, methoxylation, peroxidization, dehydration at C-20, carbonylation, dehydrogenation, cyclization, oxidation (at the double bond), and degradation. The stereochemistry of chiral centers are shown in (a) and (b).

**Table 1.** The 170 ginsenosides isolated from *P. ginseng*.

No.	Subtype	Saponins	Formula	Molecular Mass	Plant Part	Refs
1	OA <sup>1</sup>	Polyacetylene ginsenoside Ro	C <sub>65</sub> H <sub>100</sub> O <sub>21</sub>	1216.6757	Root	[44]
2	OA	Ginsenoside Ro methyl ester	C <sub>49</sub> H <sub>78</sub> O <sub>19</sub>	970.5137	Root(steamed)	[45]
3	OA	Calenduloside B	C <sub>48</sub> H <sub>78</sub> O <sub>18</sub>	942.5188	Root	[46]
4	OA	Ginsenoside Ro	C <sub>49</sub> H <sub>80</sub> O <sub>18</sub>	956.5345	Root, flower, fruit, leaf	[16,47]
5	PPD	Ginsenoside Ra1	C <sub>58</sub> H <sub>98</sub> O <sub>26</sub>	1210.6346	Root	[48]
6	PPD	Ginsenoside Ra2	C <sub>58</sub> H <sub>98</sub> O <sub>26</sub>	1210.6346	Root	[49]
7	PPD	Ginsenoside Ra3	C <sub>59</sub> H <sub>100</sub> O <sub>27</sub>	1240.6452	Root	[50]
8	PPD	Ginsenoside Rs1	C <sub>55</sub> H <sub>92</sub> O <sub>23</sub>	1120.6029	Root(steamed)	[51]
9	PPD	Ginsenoside Rs2	C <sub>55</sub> H <sub>92</sub> O <sub>23</sub>	1120.6029	Root(steamed)	[51]
10	PPD	Malonyl-ginsenoside Ra3	C <sub>62</sub> H <sub>102</sub> O <sub>30</sub>	1326.6456	Root(fresh)	[52]
11	PPD	Malonyl-notoginsenoside R4	C <sub>62</sub> H <sub>102</sub> O <sub>30</sub>	1326.6456	Root	[52]
12	PPD	Ginsenoside Ra4	C <sub>62</sub> H <sub>102</sub> O <sub>27</sub>	1278.6608	Root	[53]
13	PPD	Ginsenoside Ra5	C <sub>60</sub> H <sub>99</sub> O <sub>27</sub>	1251.6373	Root	[53]
14	PPD	Ginsenoside Ra6	C <sub>58</sub> H <sub>96</sub> O <sub>24</sub>	1176.6292	Root	[53]
15	PPD	Ginsenoside Ra7	C <sub>57</sub> H <sub>93</sub> O <sub>23</sub>	1145.6108	Root	[53]
16	PPD	Ginsenoside Ra8	C <sub>57</sub> H <sub>94</sub> O <sub>23</sub>	1146.6186	Root	[53]
17	PPD	Ginsenoside Ra9	C <sub>57</sub> H <sub>94</sub> O <sub>23</sub>	1146.6186	Root	[53]
18	PPD	20(S)-ginsenoside Rg3	C <sub>42</sub> H <sub>72</sub> O <sub>13</sub>	784.4973	Root(steamed), fruit, leaf	[54]
19	PPD	Ginsenoside Rs3	C <sub>44</sub> H <sub>74</sub> O <sub>14</sub>	826.5079	Root(steamed)	[55]
20	PPD	Ginsenoside IV	C <sub>58</sub> H <sub>96</sub> O <sub>24</sub>	1176.6292	Root	[47]
21	PPD	Ginsenoside V	C <sub>54</sub> H <sub>92</sub> O <sub>24</sub>	1124.5979	Root	[47]
22	PPD	Gypenoside-V	C <sub>54</sub> H <sub>92</sub> O <sub>22</sub>	1092.6080	Root	[46]
23	PPD	20(R)-ginsenoside Rs3	C <sub>44</sub> H <sub>74</sub> O <sub>14</sub>	826.5079	Root(steamed)	[45]
24	PPD	Acetyl-ginsenoside Rd	C <sub>50</sub> H <sub>84</sub> O <sub>19</sub>	988.5607	Root(mountain ginseng)	[56]
25	PPD	Ginsenoside F2	C <sub>42</sub> H <sub>72</sub> O <sub>13</sub>	784.4973	Root, fruit, leaf	[57]
26	PPD	Pseudoginsenoside Rc1	C <sub>50</sub> H <sub>84</sub> O <sub>19</sub>	988.5607	Fruit	[57]
27	PPD	Gypenoside XVII	C <sub>48</sub> H <sub>82</sub> O <sub>18</sub>	946.5501	Fruit, leaf	[57]
28	PPD	Gypenoside IX	C <sub>47</sub> H <sub>80</sub> O <sub>17</sub>	916.5396	Fruit, leaf	[57]
29	PPD	Quinquesoside L10	C <sub>47</sub> H <sub>80</sub> O <sub>17</sub>	916.5396	Fruit	[57]
30	PPD	25-Hydroxyprotopanaxadiol	C <sub>30</sub> H <sub>54</sub> O <sub>4</sub>	478.4022	Fruit	[58]
31	PPD	20(S)-protopanaxadiol	C <sub>30</sub> H <sub>52</sub> O <sub>3</sub>	460.3916	Fruit, leaf	[41,59]
32	PPD	20(R)-protopanaxadiol	C <sub>30</sub> H <sub>52</sub> O <sub>3</sub>	460.3916	Fruit	[59]
33	PPD	Notoginsenoside Fd	C <sub>47</sub> H <sub>80</sub> O <sub>17</sub>	916.5396	Fruit	[60]
34	PPD	Ginsenoside Rd2	C <sub>47</sub> H <sub>80</sub> O <sub>17</sub>	916.5396	Leaf	[61]
35	PPD	20(R)-ginsenoside Rg3	C <sub>42</sub> H <sub>72</sub> O <sub>13</sub>	784.4973	Root(steamed), fruit, leaf	[62,63]
36	PPD	20(S)-ginsenoside Rh2	C <sub>36</sub> H <sub>62</sub> O <sub>8</sub>	622.4445	Root(steamed), fruit, leaf	[64]
37	PPD	20(R)-ginsenoside Rh2	C <sub>36</sub> H <sub>62</sub> O <sub>8</sub>	622.4445	Fruit, leaf	[65]
38	PPD	Notoginsenoside Fe	C <sub>47</sub> H <sub>80</sub> O <sub>17</sub>	916.5396	Fruit, leaf	[61]
39	PPD	Acetyl-ginsenoside Rb1	C <sub>56</sub> H <sub>96</sub> O <sub>24</sub>	1152.6292	Root(mountain ginseng), leaf	[56]

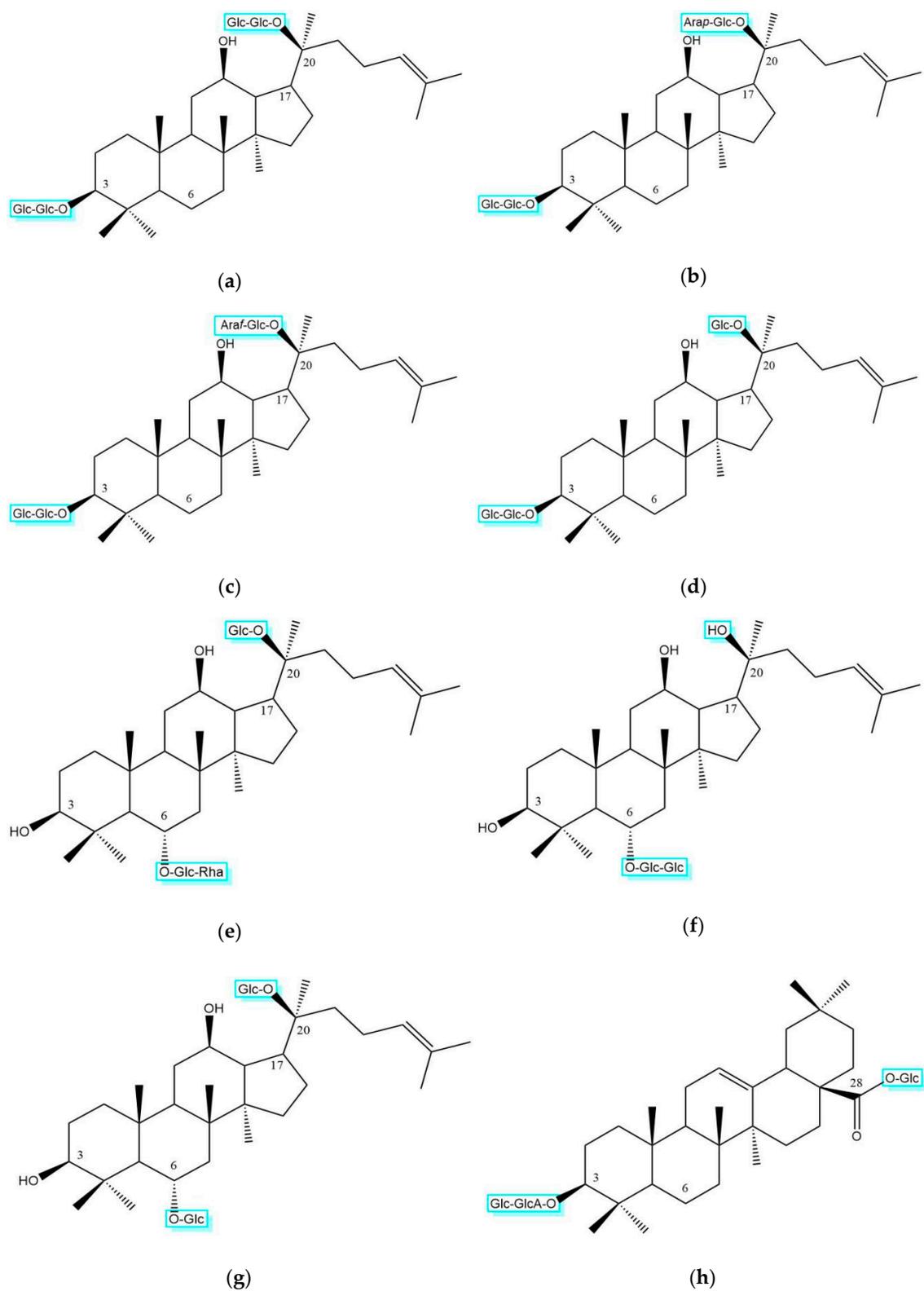
Table 1. Cont.

No.	Subtype	Saponins	Formula	Molecular Mass	Plant Part	Refs
40	PPD	Acetyl-ginsenoside Rc	C <sub>55</sub> H <sub>92</sub> O <sub>23</sub>	1120.6029	Root(mountain ginseng), leaf	[56]
41	PPD	Acetyl-ginsenoside Rb3	C <sub>55</sub> H <sub>92</sub> O <sub>23</sub>	1120.6029	Root(mountain ginseng), leaf	[56]
42	PPD	Ginsenoside compound O	C <sub>47</sub> H <sub>80</sub> O <sub>17</sub>	916.5396	Root, fruit, leaf	[16,66]
43	PPD	Malonyl-ginsenoside Rb2	C <sub>56</sub> H <sub>92</sub> O <sub>25</sub>	1164.5928	Root, flower, fruit, leaf	[16]
44	PPD	Ginsenoside Mc	C <sub>41</sub> H <sub>70</sub> O <sub>12</sub>	754.4867	Leaf	[16,66]
45	PPD	Ginsenoside compound Y	C <sub>41</sub> H <sub>70</sub> O <sub>12</sub>	754.4867	Leaf	[16]
46	PPD	Ginsenoside compound K	C <sub>36</sub> H <sub>62</sub> O <sub>8</sub>	622.4445	Root, fruit, leaf	[16]
47	PPD	Ginsenoside Rb1	C <sub>54</sub> H <sub>92</sub> O <sub>23</sub>	1108.6029	Root, flower, fruit, leaf	[16,67]
48	PPD	Malonyl-ginsenoside Rb1	C <sub>57</sub> H <sub>94</sub> O <sub>25</sub>	1178.6084	Root, flower, fruit, leaf	[16,67]
49	PPD	Ginsenoside Rc	C <sub>53</sub> H <sub>90</sub> O <sub>22</sub>	1078.5924	Root, flower, fruit, leaf	[16,67]
50	PPD	Malonyl-ginsenoside Rc	C <sub>56</sub> H <sub>92</sub> O <sub>25</sub>	1164.5928	Root, flower, fruit, leaf	[16,67]
51	PPD	Ginsenoside Rb2	C <sub>53</sub> H <sub>90</sub> O <sub>22</sub>	1078.5924	Root, flower, fruit, leaf	[16,67]
52	PPD	Ginsenoside Rb3	C <sub>53</sub> H <sub>90</sub> O <sub>22</sub>	1078.5924	Root, flower, fruit, leaf	[16,67]
53	PPD	Malonyl-ginsenoside Rb3	C <sub>56</sub> H <sub>92</sub> O <sub>25</sub>	1164.5928	Root, flower, leaf	[16,67]
54	PPD	Ginsenoside Rd	C <sub>48</sub> H <sub>82</sub> O <sub>18</sub>	946.5501	Root, flower, fruit, leaf	[16,67]
55	PPD	Malonyl-ginsenoside Rd	C <sub>51</sub> H <sub>84</sub> O <sub>21</sub>	1032.5505	Root, flower, fruit, leaf	[16,67]
56	PPD	Malonyl-floralginsenoside Rd2	C <sub>51</sub> H <sub>84</sub> O <sub>21</sub>	1032.5505	Flower	[68]
57	PPD	Malonyl-floralginsenoside Rd3	C <sub>51</sub> H <sub>84</sub> O <sub>21</sub>	1032.5505	Flower	[68]
58	PPD	Malonyl-floralginsenoside Rd4	C <sub>51</sub> H <sub>84</sub> O <sub>21</sub>	1032.5505	Flower	[68]
59	PPD	Malonyl-floralginsenoside Rd5	C <sub>51</sub> H <sub>84</sub> O <sub>21</sub>	1032.5505	Flower	[68]
60	PPD	Malonyl-floralginsenoside Rd6	C <sub>54</sub> H <sub>87</sub> O <sub>24</sub>	1119.5587	Flower	[68]
61	PPD	Malonyl-floralginsenoside Rc2	C <sub>56</sub> H <sub>92</sub> O <sub>25</sub>	1164.5928	Flower	[68]
62	PPD	Malonyl-floralginsenoside Rc3	C <sub>56</sub> H <sub>92</sub> O <sub>25</sub>	1164.5928	Flower	[68]
63	PPD	Malonyl-floralginsenoside Rc4	C <sub>56</sub> H <sub>92</sub> O <sub>25</sub>	1164.5928	Flower	[68]
64	PPT	20(S)-ginsenoside Rg2	C <sub>42</sub> H <sub>72</sub> O <sub>13</sub>	784.4973	Root, fruit, leaf	[54,69]
65	PPT	Koryoginsenoside R1	C <sub>46</sub> H <sub>76</sub> O <sub>15</sub>	868.5184	Root	[36]
66	PPT	Ginsenoside Re6	C <sub>46</sub> H <sub>76</sub> O <sub>15</sub>	868.5184	Root	[70]
67	PPT	Ginsenoside Re2	C <sub>48</sub> H <sub>82</sub> O <sub>19</sub>	962.5450	Root	[70]
68	PPT	Ginsenoside Re3	C <sub>48</sub> H <sub>82</sub> O <sub>19</sub>	962.5450	Root	[70]
69	PPT	Ginsenoside Re4	C <sub>47</sub> H <sub>80</sub> O <sub>18</sub>	932.5345	Root	[70]
70	PPT	Notoginsenoside Rt	C <sub>44</sub> H <sub>74</sub> O <sub>15</sub>	842.5028	Root	[46]
71	PPT	Majoroside F6	C <sub>48</sub> H <sub>82</sub> O <sub>19</sub>	962.5450	Root	[46]
72	PPT	Pseudoginsenoside Rt3	C <sub>42</sub> H <sub>70</sub> O <sub>13</sub>	782.4816	Root	[46]
73	PPT	Vinaginsenoside R15	C <sub>42</sub> H <sub>72</sub> O <sub>15</sub>	816.4871	Root	[46]
74	PPT	20(R)-ginsenoside Rf	C <sub>42</sub> H <sub>72</sub> O <sub>14</sub>	800.4922	Root	[45]
75	PPT	20(R)-notoginsenoside R2	C <sub>41</sub> H <sub>70</sub> O <sub>13</sub>	770.4816	Root	[45]
76	PPT	Ginsenoside Ia	C <sub>42</sub> H <sub>72</sub> O <sub>14</sub>	800.4922	Fruit	[71]
77	PPT	Chikusetsusaponin LM1	C <sub>41</sub> H <sub>70</sub> O <sub>13</sub>	770.4816	Fruit	[57]
78	PPT	25-Hydroxyprotopanaxatriol	C <sub>30</sub> H <sub>54</sub> O <sub>5</sub>	494.3971	Fruit	[58]
79	PPT	20(S)-protopanaxatriol	C <sub>30</sub> H <sub>52</sub> O <sub>4</sub>	476.3866	Fruit, leaf	[59]
80	PPT	20(R)-protopanaxatriol	C <sub>30</sub> H <sub>52</sub> O <sub>4</sub>	476.3866	Fruit	[59]
81	PPT	Notoginsenoside R3	C <sub>48</sub> H <sub>82</sub> O <sub>19</sub>	962.5450	Fruit	[60]
82	PPT	20-gluco-ginsenoside Rf	C <sub>48</sub> H <sub>82</sub> O <sub>19</sub>	962.5450	Root, flower, leaf	[16]
83	PPT	Saponin IIb	C <sub>36</sub> H <sub>62</sub> O <sub>9</sub>	638.4394	Leaf	[72]
84	PPT	Saponin IIIc	C <sub>37</sub> H <sub>62</sub> O <sub>10</sub>	666.4343	Leaf	[72]
85	PPT	20(S)-ginsenoside Rh1	C <sub>36</sub> H <sub>62</sub> O <sub>9</sub>	638.4394	Leaf	[62]
86	PPT	20(R)-ginsenoside Rh1	C <sub>36</sub> H <sub>62</sub> O <sub>9</sub>	638.4394	Root(steamed), leaf	[21]
87	PPT	Acetyl-ginsenoside Rg1	C <sub>44</sub> H <sub>74</sub> O <sub>15</sub>	842.5028	Root(mountain ginseng), leaf	[56]
88	PPT	Acetyl-ginsenoside Re	C <sub>50</sub> H <sub>84</sub> O <sub>19</sub>	988.5607	Root(mountain ginseng), leaf	[56]
89	PPT	Notoginsenoside R2	C <sub>41</sub> H <sub>70</sub> O <sub>13</sub>	770.4816	Root, fruit, leaf	[16]
90	PPT	Notoginsenoside R1	C <sub>47</sub> H <sub>80</sub> O <sub>18</sub>	932.5345	Root, flower, fruit, leaf	[16,67]
91	PPT	Ginsenoside Rg1	C <sub>42</sub> H <sub>72</sub> O <sub>14</sub>	800.4922	Root, flower, fruit, leaf	[16,67]
92	PPT	Ginsenoside Re	C <sub>48</sub> H <sub>82</sub> O <sub>18</sub>	946.5501	Root, flower, fruit, leaf	[16,67]
93	PPT	Malonyl-ginsenoside Rg1	C <sub>45</sub> H <sub>74</sub> O <sub>17</sub>	886.4926	Root, flower, leaf	[16,67]
94	PPT	Malonyl-ginsenoside Re	C <sub>51</sub> H <sub>84</sub> O <sub>21</sub>	1032.5505	Root, flower, fruit, leaf	[16,67]
95	PPT	Ginsenoside Rf	C <sub>42</sub> H <sub>72</sub> O <sub>14</sub>	800.4922	Root, flower, fruit, leaf	[16,67]
96	PPT	20(R)-ginsenoside Rg2	C <sub>42</sub> H <sub>72</sub> O <sub>13</sub>	784.4973	Root(steamed), flower, fruit, leaf	[16,67]
97	PPT	Ginsenoside Rf3	C <sub>41</sub> H <sub>70</sub> O <sub>13</sub>	770.4816	Flower	[67]
98	PPT	Floralginsenoside M	C <sub>53</sub> H <sub>90</sub> O <sub>22</sub>	1078.5924	Flower, leaf	[73]
99	PPT	Floralginsenoside N	C <sub>53</sub> H <sub>90</sub> O <sub>22</sub>	1078.5924	Flower, leaf	[73]
100	PPT	Floralginsenoside P	C <sub>53</sub> H <sub>90</sub> O <sub>23</sub>	1094.5873	Flower	[73]
101	PPT	Ginsenoside F1	C <sub>36</sub> H <sub>62</sub> O <sub>9</sub>	638.4394	Flower, fruit, leaf	[74]
102	PPT	Ginsenoside F3	C <sub>41</sub> H <sub>70</sub> O <sub>13</sub>	770.4816	Flower, fruit, leaf	[74]
103	PPT	Ginsenoside F5	C <sub>41</sub> H <sub>70</sub> O <sub>13</sub>	770.4816	Flower, fruit, leaf	[74]
104	PPT	Malonyl-floralginsenoside Re2	C <sub>51</sub> H <sub>84</sub> O <sub>21</sub>	1032.5505	Flower	[68]
105	PPT	Malonyl-floralginsenoside Re3	C <sub>51</sub> H <sub>84</sub> O <sub>21</sub>	1032.5505	Flower	[68]
106	C17SCV	Koryoginsenoside R2	C <sub>54</sub> H <sub>92</sub> O <sub>24</sub>	1124.5979	Root	[36]
107	C17SCV	Ginsenoside Re5	C <sub>42</sub> H <sub>72</sub> O <sub>15</sub>	816.4871	Root	[70]
108	C17SCV	Ginsenoside Rs4	C <sub>44</sub> H <sub>72</sub> O <sub>13</sub>	808.4973	Root(sun cured)	[75]
109	C17SCV	Dehydroprotopanaxadiol I	C <sub>30</sub> H <sub>50</sub> O <sub>2</sub>	442.3811	Root(steamed)	[2]

Table 1. Cont.

No.	Subtype	Saponins	Formula	Molecular Mass	Plant Part	Refs
110	C17SCV	Ginsenoside Rg5	C <sub>42</sub> H <sub>70</sub> O <sub>12</sub>	766.4867	Root(steamed)	[76]
111	C17SCV	Dehydroprotopanaxatriol I	C <sub>30</sub> H <sub>50</sub> O <sub>3</sub>	458.3760	Root(steamed)	[2]
112	C17SCV	Ginsenoside Rs6	C <sub>38</sub> H <sub>62</sub> O <sub>9</sub>	662.4394	Root(sun cured)	[75]
113	C17SCV	Ginsenoside Rz1	C <sub>42</sub> H <sub>70</sub> O <sub>12</sub>	766.4867	Root(steamed)	[77]
114	C17SCV	Dehydroprotopanaxadiol II	C <sub>30</sub> H <sub>50</sub> O <sub>2</sub>	442.3811	Root(steamed)	[2]
115	C17SCV	Ginsenoside Rs5	C <sub>44</sub> H <sub>72</sub> O <sub>13</sub>	808.4973	Root(sun cured)	[75]
116	C17SCV	Dehydroprotopanaxatriol II	C <sub>30</sub> H <sub>50</sub> O <sub>3</sub>	458.3760	Root(steamed)	[2]
117	C17SCV	Ginsenoside Rg6	C <sub>42</sub> H <sub>70</sub> O <sub>12</sub>	766.4867	Root(steamed)	[78]
118	C17SCV	Ginsenoside Rk3	C <sub>36</sub> H <sub>60</sub> O <sub>8</sub>	620.4288	Root(steamed)	[76]
119	C17SCV	Ginsenoside Rs7	C <sub>38</sub> H <sub>62</sub> O <sub>9</sub>	662.4394	Root(sun cured)	[75]
120	C17SCV	Ginsenoside Rg9	C <sub>42</sub> H <sub>70</sub> O <sub>13</sub>	782.4816	Root(steamed)	[79]
121	C17SCV	12-O-glucoginsenoside Rh4	C <sub>42</sub> H <sub>70</sub> O <sub>13</sub>	782.4816	Root(steamed)	[80]
122	C17SCV	Ginsenoside Rg10	C <sub>42</sub> H <sub>69</sub> O <sub>13</sub>	781.4738	Root(steamed)	[79]
123	C17SCV	Ginsenoside Rh10	C <sub>36</sub> H <sub>62</sub> O <sub>8</sub>	622.4445	Root(steamed)	[80]
124	C17SCV	Ginsenoside Rg11	C <sub>42</sub> H <sub>70</sub> O <sub>14</sub>	798.4766	Root(steamed)	[80]
125	C17SCV	Vinaginsenoside R8	C <sub>48</sub> H <sub>82</sub> O <sub>19</sub>	962.5450	Fruit	[57]
126	C17SCV	Ginsenoside Rh4	C <sub>36</sub> H <sub>60</sub> O <sub>8</sub>	620.4288	Root(steamed), fruit	[4,57]
127	C17SCV	Ginsenoside Rh5	C <sub>36</sub> H <sub>60</sub> O <sub>9</sub>	636.4237	Root(steamed), fruit	[4,57]
128	C17SCV	Isoginsenoside-Rh3	C <sub>36</sub> H <sub>60</sub> O <sub>7</sub>	604.4339	Fruit	[81]
129	C17SCV	Ginsenoside Rf2	C <sub>42</sub> H <sub>72</sub> O <sub>14</sub>	800.4922	Fruit	[82]
130	C17SCV	Ginsenoside Rk2	C <sub>36</sub> H <sub>60</sub> O <sub>7</sub>	604.4339	Root(steamed), fruit	[76,83]
131	C17SCV	Pseudoginsenoside RT5	C <sub>36</sub> H <sub>62</sub> O <sub>10</sub>	654.4343	Fruit	[83]
132	C17SCV	Ginsenoside Rh3	C <sub>36</sub> H <sub>60</sub> O <sub>7</sub>	604.4339	Root(steamed), fruit	[76,83]
133	C17SCV	Ginsenoside Rg4	C <sub>42</sub> H <sub>70</sub> O <sub>12</sub>	766.4867	Root, fruit	[16]
134	C17SCV	Ginsenoside F4	C <sub>42</sub> H <sub>70</sub> O <sub>12</sub>	766.4867	Root, fruit, leaf	[16]
135	C17SCV	Ginsenoside Rg7	C <sub>36</sub> H <sub>60</sub> O <sub>9</sub>	636.4237	Leaf	[39]
136	C17SCV	Ginsenoside Rh6	C <sub>36</sub> H <sub>62</sub> O <sub>11</sub>	670.4292	Fruit, leaf	[39]
137	C17SCV	Ginsenoside Ki	C <sub>36</sub> H <sub>62</sub> O <sub>10</sub>	654.4343	Leaf	[39]
138	C17SCV	Ginsenoside Km	C <sub>36</sub> H <sub>62</sub> O <sub>10</sub>	654.4343	Leaf	[84]
139	C17SCV	Ginsenoside Rh9	C <sub>36</sub> H <sub>60</sub> O <sub>9</sub>	636.4237	Leaf	[39]
140	C17SCV	12,23-Epoxyginsenoside Rg1	C <sub>42</sub> H <sub>70</sub> O <sub>14</sub>	798.4766	Leaf	[85]
141	C17SCV	Ginsenoside Rh7	C <sub>36</sub> H <sub>60</sub> O <sub>9</sub>	636.4237	Leaf	[39]
142	C17SCV	Ginsenoside Rh8	C <sub>36</sub> H <sub>60</sub> O <sub>9</sub>	636.4237	Leaf	[39]
143	C17SCV	Hexanordammaran	C <sub>24</sub> H <sub>40</sub> O <sub>4</sub>	392.2927	Leaf	[86]
144	C17SCV	Floralginsenoside A	C <sub>42</sub> H <sub>72</sub> O <sub>16</sub>	832.4820	Flower	[87]
145	C17SCV	Ginsenoside La	C <sub>42</sub> H <sub>70</sub> O <sub>13</sub>	782.4816	Leaf	[35]
146	C17SCV	Vinaginsenoside R4	C <sub>48</sub> H <sub>82</sub> O <sub>19</sub>	962.5450	Root, fruit, leaf	[16]
147	C17SCV	Ginsenoside Rk1	C <sub>42</sub> H <sub>70</sub> O <sub>12</sub>	766.4867	Root(steamed), fruit, leaf	[16]
148	C17SCV	Floralginsenoside H	C <sub>50</sub> H <sub>84</sub> O <sub>21</sub>	1020.5505	Flower	[88]
149	C17SCV	Floralginsenoside Tc	C <sub>53</sub> H <sub>90</sub> O <sub>24</sub>	1110.5822	Flower	[89]
150	C17SCV	Floralginsenoside Td	C <sub>53</sub> H <sub>90</sub> O <sub>24</sub>	1110.5822	Flower	[84]
151	C17SCV	Ginsenoside I	C <sub>48</sub> H <sub>82</sub> O <sub>20</sub>	978.5400	Flower	[90]
152	C17SCV	Ginsenoside II	C <sub>48</sub> H <sub>82</sub> O <sub>20</sub>	978.5400	Flower	[90]
153	C17SCV	Floralginsenoside C	C <sub>41</sub> H <sub>70</sub> O <sub>15</sub>	802.4715	Flower	[74]
154	C17SCV	Floralginsenoside J	C <sub>48</sub> H <sub>82</sub> O <sub>20</sub>	978.5400	Flower	[88]
155	C17SCV	Floralginsenoside Ka	C <sub>36</sub> H <sub>62</sub> O <sub>11</sub>	670.4292	Flower	[91]
156	C17SCV	Floralginsenoside La	C <sub>48</sub> H <sub>82</sub> O <sub>19</sub>	962.5450	Flower	[88]
157	C17SCV	Floralginsenoside Lb	C <sub>48</sub> H <sub>82</sub> O <sub>19</sub>	962.5450	Flower	[88]
158	C17SCV	Floralginsenoside Ta	C <sub>36</sub> H <sub>60</sub> O <sub>10</sub>	652.4187	Flower	[89]
159	C17SCV	Floralginsenoside E	C <sub>42</sub> H <sub>72</sub> O <sub>15</sub>	816.4871	Flower	[74]
160	C17SCV	Floralginsenoside F	C <sub>42</sub> H <sub>72</sub> O <sub>15</sub>	816.4871	Flower	[74]
161	C17SCV	Floralginsenoside G	C <sub>50</sub> H <sub>84</sub> O <sub>21</sub>	1020.5505	Flower	[88]
162	C17SCV	Floralginsenoside K	C <sub>48</sub> H <sub>82</sub> O <sub>21</sub>	994.5349	Flower	[88]
163	C17SCV	Floralginsenoside O	C <sub>53</sub> H <sub>90</sub> O <sub>22</sub>	1078.5924	Flower	[73]
164	C17SCV	Floralginsenoside B	C <sub>42</sub> H <sub>72</sub> O <sub>16</sub>	832.4820	Flower	[74]
165	C17SCV	Floralginsenoside D	C <sub>41</sub> H <sub>70</sub> O <sub>15</sub>	802.4715	Flower	[74]
166	C17SCV	Floralginsenoside I	C <sub>48</sub> H <sub>82</sub> O <sub>20</sub>	978.5400	Flower	[88]
167	C17SCV	Floralginsenoside Kb	C <sub>45</sub> H <sub>76</sub> O <sub>19</sub>	920.4981	Flower	[91]
168	C17SCV	Floralginsenoside Kc	C <sub>45</sub> H <sub>76</sub> O <sub>20</sub>	936.4930	Flower	[91]
169	C17SCV	Floralginsenoside Tb	C <sub>35</sub> H <sub>62</sub> O <sub>11</sub>	658.4292	Flower	[89]
170	C17SCV	Ginsenoside III	C <sub>48</sub> H <sub>80</sub> O <sub>19</sub>	960.5294	Flower	[92]

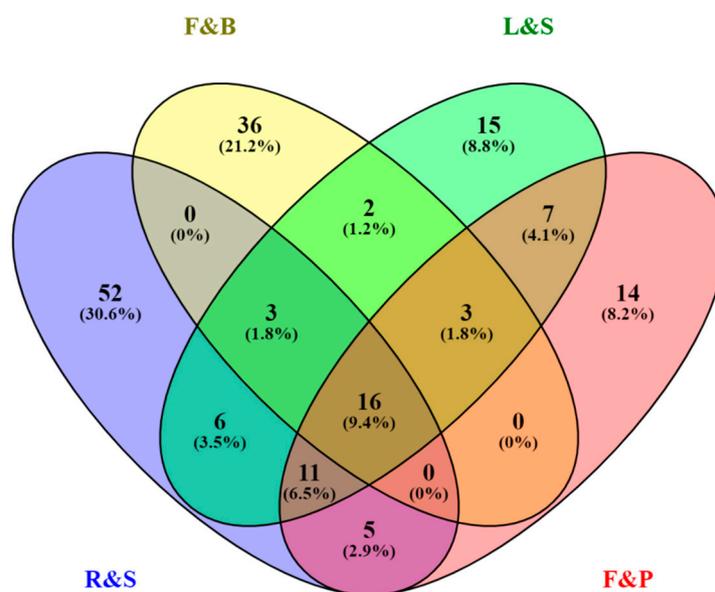
<sup>1</sup> OA: Oleanolic acid; PPD: Protopanaxadiol; PPT: Protopanaxatriol; C17SCV: C17 side-chain varied.



**Figure 2.** Structures of eight high-abundance saponins in *P. ginseng*. (a) PPD-type ginsenoside Rb1; (b) PPD-type ginsenoside Rb2; (c) PPD-type ginsenoside Rc; (d) PPD-type ginsenoside Rd; (e) PPT-type ginsenoside Re; (f) PPT-type ginsenoside Rf; (g) PPT-type ginsenoside Rg1; (h) OA-type ginsenoside Ro.

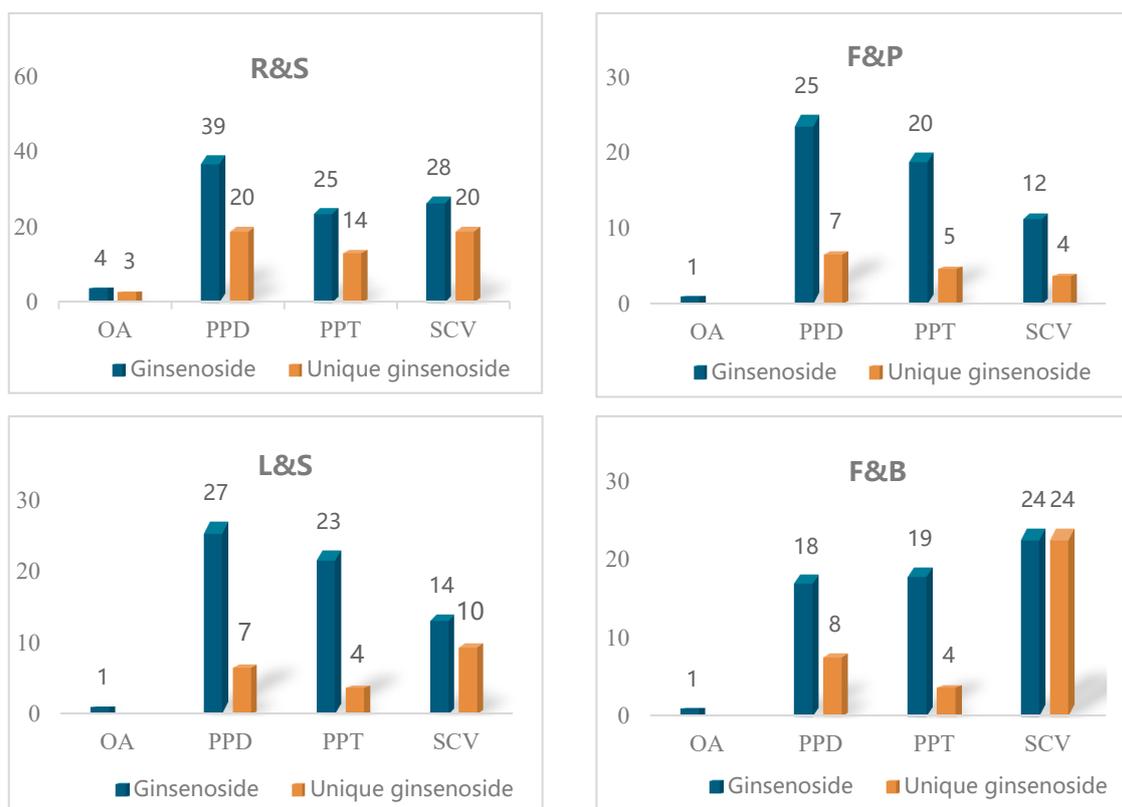
#### 4. Spatial Distribution of Ginsenosides in Different Parts

The Venn diagram (Figure 3) shows the number of ginsenosides commonly and separately shared by the following four groups: R&S (roots, rhizomes, and steamed roots), L&S (leaves and stems), F&P (fruits and fruit pedicels), and F&B (flowers and flower buds). Among them, the number of unique ginsenosides in group R&S, F&P, L&S, and F&B are 52, 15, 14, and 36, respectively, accounting for 30.6%, 8.8%, 8.2%, and 21.2% of the number of total ginsenosides, respectively. The result gives some explanation why ginseng root is designated as medicinal parts rather than the other parts. Sixteen ginsenosides are commonly existed in all tissues, and among them, there are nine PPD type (Rc, Rd, Rb2, Rb1, Rb3, m-ginsenoside Rb1, m-ginsenoside Rc, m-ginsenoside Rb2, m-ginsenoside Rd), six PPT type (Re, Rg1, Rf, 20(R)-ginsenoside Rg2, Notoginsenoside R1, m-ginsenoside Re), one OA type (Ro), and none of C17SCV type. Numbers of ginsenosides shared by R&S and F&P, F&P and L&S, L&S and F&B, R&S and F&B were 32 (18.8%), 37 (21.7%), 24 (14.1%), and 19 (11.2%), respectively. In addition, 13 malonyl-ginsenosides were existing specifically in flowers and buds; however, none of them was observed in fruit. This implies that these malonyl-ginsenosides show not only spatial specificity, but also temporal specificity. Here in, we speculate that malonyl-ginsenosides may play a physiological role during tissue development.



**Figure 3.** Venn diagram of ginsenosides according to different parts of *P. ginseng*. R&S: Roots, rhizomes, and steamed roots; L&S: Leaves and stems; F&P: Fruits and fruit pedicels; F&B: Flowers and flower buds.

As indicated by Figure 4, the numbers of PPD-type ginsenosides (blue bar) are highest in R&S, F&P, and L&S, while the C17SCV-type ginsenoside is highest in F&B. Interestingly, C17SCV-type ginsenosides exhibit significant variation among different groups. Only nine C17SCV-type ginsenosides are shared by more than two groups, whereas the other 58 C17SCV-type ginsenosides are unique to a particular group. For the OA-type ginsenoside, three are specific to group R&S (Polyacetyleneginsenoside-Ro, Ginsenoside Ro methyl ester, Calendulose-B) and one (Ginsenoside Ro) is commonly shared by all parts.



**Figure 4.** Structural categories of ginsenosides in different parts of *P. ginseng*. R&S: Roots, rhizomes, and steamed roots; F&P: Fruits and fruit pedicels; L&S: Leaves and stems; F&B: Flowers and flower buds; OA: Oleanolic acid; PPD: Protopanaxadiol; PPT: Protopanaxatriol; C17SCV: C17 side-chain varied.

## 5. Isomers of Ginsenosides

The total 170 ginsenosides are divided into 69 molecular formula groups. Therefore, it is common that one molecular formula corresponds to several ginsenosides. (Table 2). The molecular formula with the largest number of isomers is  $C_{48}H_{82}O_{19}$  (molecular weight 962.5450), with a total of nine isomers; followed by  $C_{51}H_{84}O_{21}$  (molecular weight 1032.5505) with a total of eight isomers, and  $C_{41}H_{70}O_{13}$  (molecular weight 770.4816) with a total of seven isomers. The isomers median of 69 molecular formulas is 2, which means that one molecular formula corresponds to two isomers equally. Optical and position isomerism are the dominant types of ginsenoside isomers, whilst cis-trans isomerism and tautomerism are detected occasionally.

Table 2. Isomers of 170 ginseng saponins.

No.	Formula	Molecular Mass	No. of Isomers	No.	Formula	Molecular Mass	No. of Isomers
1	C <sub>24</sub> H <sub>40</sub> O <sub>4</sub>	392.2927	1	36	C <sub>46</sub> H <sub>76</sub> O <sub>15</sub>	868.5184	2
2	C <sub>30</sub> H <sub>50</sub> O <sub>2</sub>	442.3811	2	37	C <sub>47</sub> H <sub>80</sub> O <sub>17</sub>	916.5396	6
3	C <sub>30</sub> H <sub>50</sub> O <sub>3</sub>	458.3760	2	38	C <sub>47</sub> H <sub>80</sub> O <sub>18</sub>	932.5345	2
4	C <sub>30</sub> H <sub>52</sub> O <sub>3</sub>	460.3916	2	39	C <sub>48</sub> H <sub>78</sub> O <sub>18</sub>	942.5188	1
5	C <sub>30</sub> H <sub>52</sub> O <sub>4</sub>	476.3866	2	40	C <sub>48</sub> H <sub>80</sub> O <sub>19</sub>	960.5294	1
6	C <sub>30</sub> H <sub>54</sub> O <sub>4</sub>	478.4022	1	41	C <sub>48</sub> H <sub>82</sub> O <sub>18</sub>	946.5501	3
7	C <sub>30</sub> H <sub>54</sub> O <sub>5</sub>	494.3971	1	42	C <sub>48</sub> H <sub>82</sub> O <sub>19</sub>	962.5450	9
8	C <sub>35</sub> H <sub>62</sub> O <sub>11</sub>	658.4292	1	43	C <sub>48</sub> H <sub>82</sub> O <sub>20</sub>	978.5400	4
9	C <sub>36</sub> H <sub>60</sub> O <sub>10</sub>	652.4187	1	44	C <sub>48</sub> H <sub>82</sub> O <sub>21</sub>	994.5349	1
10	C <sub>36</sub> H <sub>60</sub> O <sub>7</sub>	604.4339	3	45	C <sub>49</sub> H <sub>78</sub> O <sub>19</sub>	970.5137	1
11	C <sub>36</sub> H <sub>60</sub> O <sub>8</sub>	620.4288	2	46	C <sub>49</sub> H <sub>80</sub> O <sub>18</sub>	956.5345	1
12	C <sub>36</sub> H <sub>60</sub> O <sub>9</sub>	636.4237	5	47	C <sub>50</sub> H <sub>84</sub> O <sub>19</sub>	988.5607	3
13	C <sub>36</sub> H <sub>62</sub> O <sub>10</sub>	654.4343	3	48	C <sub>50</sub> H <sub>84</sub> O <sub>21</sub>	1020.5505	2
14	C <sub>36</sub> H <sub>62</sub> O <sub>11</sub>	670.4292	2	49	C <sub>51</sub> H <sub>84</sub> O <sub>21</sub>	1032.5505	8
15	C <sub>36</sub> H <sub>62</sub> O <sub>8</sub>	622.4445	4	50	C <sub>53</sub> H <sub>90</sub> O <sub>22</sub>	1078.5924	6
16	C <sub>36</sub> H <sub>62</sub> O <sub>9</sub>	638.4394	4	51	C <sub>53</sub> H <sub>90</sub> O <sub>23</sub>	1094.5873	1
17	C <sub>37</sub> H <sub>62</sub> O <sub>10</sub>	666.4343	1	52	C <sub>53</sub> H <sub>90</sub> O <sub>24</sub>	1110.5822	2
18	C <sub>38</sub> H <sub>62</sub> O <sub>9</sub>	662.4394	2	53	C <sub>54</sub> H <sub>92</sub> O <sub>24</sub>	1119.5587	1
19	C <sub>41</sub> H <sub>70</sub> O <sub>12</sub>	754.4867	2	54	C <sub>54</sub> H <sub>92</sub> O <sub>22</sub>	1092.6080	1
20	C <sub>41</sub> H <sub>70</sub> O <sub>13</sub>	770.4816	7	55	C <sub>54</sub> H <sub>92</sub> O <sub>23</sub>	1108.6029	1
21	C <sub>41</sub> H <sub>70</sub> O <sub>15</sub>	802.4715	2	56	C <sub>54</sub> H <sub>92</sub> O <sub>24</sub>	1124.5979	2
22	C <sub>42</sub> H <sub>69</sub> O <sub>13</sub>	781.4738	1	57	C <sub>55</sub> H <sub>92</sub> O <sub>23</sub>	1120.6029	4
23	C <sub>42</sub> H <sub>70</sub> O <sub>12</sub>	766.4867	6	58	C <sub>56</sub> H <sub>92</sub> O <sub>25</sub>	1164.5928	6
24	C <sub>42</sub> H <sub>70</sub> O <sub>13</sub>	782.4816	4	59	C <sub>56</sub> H <sub>96</sub> O <sub>24</sub>	1152.6292	1
25	C <sub>42</sub> H <sub>70</sub> O <sub>14</sub>	798.4766	2	60	C <sub>57</sub> H <sub>93</sub> O <sub>23</sub>	1145.6108	1
26	C <sub>42</sub> H <sub>72</sub> O <sub>13</sub>	784.4973	5	61	C <sub>57</sub> H <sub>94</sub> O <sub>23</sub>	1146.6186	2
27	C <sub>42</sub> H <sub>72</sub> O <sub>14</sub>	800.4922	5	62	C <sub>57</sub> H <sub>94</sub> O <sub>25</sub>	1178.6084	1
28	C <sub>42</sub> H <sub>72</sub> O <sub>15</sub>	816.4871	4	63	C <sub>58</sub> H <sub>96</sub> O <sub>24</sub>	1176.6292	2
29	C <sub>42</sub> H <sub>72</sub> O <sub>16</sub>	832.4820	2	64	C <sub>58</sub> H <sub>98</sub> O <sub>26</sub>	1210.6346	2
30	C <sub>44</sub> H <sub>72</sub> O <sub>13</sub>	808.4973	2	65	C <sub>59</sub> H <sub>100</sub> O <sub>27</sub>	1240.6452	1
31	C <sub>44</sub> H <sub>74</sub> O <sub>14</sub>	826.5079	2	66	C <sub>60</sub> H <sub>99</sub> O <sub>27</sub>	1251.6373	1
32	C <sub>44</sub> H <sub>74</sub> O <sub>15</sub>	842.5028	2	67	C <sub>62</sub> H <sub>102</sub> O <sub>27</sub>	1278.6608	1
33	C <sub>45</sub> H <sub>74</sub> O <sub>17</sub>	886.4926	1	68	C <sub>62</sub> H <sub>102</sub> O <sub>30</sub>	1326.6456	2
34	C <sub>45</sub> H <sub>76</sub> O <sub>19</sub>	920.4981	1	69	C <sub>65</sub> H <sub>100</sub> O <sub>21</sub>	1216.6757	1
35	C <sub>45</sub> H <sub>76</sub> O <sub>20</sub>	936.4930	1				

## 6. Mass Spectrometry-Based Metabolomics Analysis on *P. ginseng*

Recently, MS and its hyphenations with chromatographic separation techniques have emerged as an instrumental trend in ginsenoside analysis [93,94]. HPLC/MS can overcome the problems related to ginsenoside pre-analysis derivatization and the low abundance of molecular ions [95,96]. The use of on-line MS detection shows superior sensitivity and specificity compared with conventional UV and ELSD detection [97,98]. The sensitivity of MS detection can surpass 1000 times that of UV absorbance [99]. In addition, the possible matrix effects encountered with many *Panax ginseng* formulations may be compromised by MS [100]. Despite these advantages, MS remains costly for use in routine analysis. With the development of soft ionization techniques, HPLC/MS has been successfully applied for the qualitative and quantitative analyses of *Panax ginseng* [101]. Among the various mass spectrometry ionization techniques, electrospray mass spectrometry (ESI-MS) is the approach that is most commonly coupled with HPLC [15,102,103]. While ESI-MS suffers from matrix-induced ionization suppression difficulties [104], atmospheric pressure chemical ionization (APCI) can offer itself as one possible alternative [105]. Quadrupole time-of-flight mass spectrometry (QTOF-MS), a powerful tool for the identification of analytes, provides several advantages in structural analysis, such as a higher resolution and accuracy in mass measurements. Coupled with QTOF-MS, UPLC has been introduced for metabolite profiling and metabolomics purposes [99]. In recent years, orbitrap technology has achieved great breakthrough in resolution and scanning speed and realized the high-resolution detection of multi-stage mass spectrometry by combining the linear ion trap and quadrupole mass spectrometry, which can be widely applied in the development of new drugs [106].

According to the available literature, Wang et al. in 1999 [97] firstly identified ginsenosides by LC/MS/MS and differentiated *P. ginseng* and *P. quinquefolius* based on the ginsenoside Rg1/Rf and Rc/Rb2 ratios. A liquid chromatography-tandem mass spectrometry (LC/MS/MS) method was developed to distinguish Asian ginseng and North American ginseng. The method is based on the baseline chromatographic separation of two potential chemical markers: Rf and 24(R)-pseudo ginsenoside F11 [107]. Z X. et al. 2000 developed a similar LC/MS/MS method to determine ginsenoside in ginseng. Nine ginsenosides were determined, among which five of them were identified according to molecular

weight [108]. In the late 1990s and early 2000s, the resolution of mass spectrometry was low and the number of identified ginsenosides was limited, which could be used for distinguishing Asian ginseng and American Ginseng, and identifying ginsenosides.

Chen et al. [109] established a chemical finger-print metabolomics approach using ultra-high-performance liquid chromatography combined with quadrupole time-of-flight mass spectrometry (UPLC-QTOF/MS). The method was successfully used to authenticate and evaluate *Panax Ginseng* of various commercial grades. Using UPLC-QTOF-MS/MS, Zhang et al. evaluated the overall quality of commercially available white ginseng and red ginseng, and investigated their characteristic chemical composition indicators. Fifty-one major chromatographic peaks of white ginseng and red ginseng samples were separated within 24 min [110]. By means of UPLC-DAD-QTOF-MS/MS, Wang et al. conducted qualitative and quantitative analysis of ginsenosides of cultivated ginseng and mountain ginseng. A total of 131 ginsenosides were detected in cultivated ginseng and mountain ginseng, and all the components were completely separated within 10 min, among which contents of 19 typical ginsenoside were accurately quantified. This method has been validated for quality evaluation of ginseng and identification of cultivated ginseng and mountain ginseng [13]. Zhang et al. Quickly and comprehensively identified the ginsenosides using high-resolution time-of-flight mass spectrometry, electrospray dual-spray ion source, and negative ion mode. A total of 95 saponins in suncured ginseng were identified within 11 min, providing a feasible basis for the quality control of suncured ginseng [111]. With the emergence of high-resolution mass spectrometry and the development of high-throughput screening technologies, several time-saving methods were established for commercial ginseng product evaluation.

Since 2015, Orbitrap mass spectrometer had been applied in ginsenoside detection. In 2017, a total of 101 malonyl-ginsenosides were firstly systematic analyzed by hybrid LTQ-Orbitrap mass spectrometer after UHPLC separation, and ten potential malonyl-ginsenoside markers were discovered for the discrimination of *P. ginseng*, *P. quinquefolius*, and *P. notoginseng* [112]. Shi et al. established an untargeted profiling strategy on a linear ion-trap/Orbitrap mass spectrometer coupled to ultra-high performance liquid chromatography to analyze malonyl-ginsenosides in several *Panax* species. Finally, 178 malonyl-ginsenosides were characterized from roots, leaves, and flower buds of *P. ginseng*, *P. quinquefolius*, and *P. notoginseng* [113]. To investigate the variation of ginsenosides among different processed red ginseng, Zhong et al. tested steamed, vinegared and dried red ginseng samples by UPLC-Q-Orbitrap MS. In total, 32 ginsenosides were identified and ginsenosides m-Rb1, Rh1, F1, 20(R)-Rh1, Rg5, and Rs5 were only found in red ginseng processed by vinegar [114]. With the development of Orbitrap and multi-mass spectrometry techniques, ginsenosides with complex structures, such as malonyl and C17 side-chain variation, have been increasingly detected, and the types of ginsenosides have been greatly extended.

## 7. Conclusions

In this review, we summarized the existing studies related to saponin analysis of *P. ginseng*, and sorted out the information of structural characteristic, spatial distribution, and isomer of 170 ginsenosides. There are 16 common ginsenosides present in all parts of *P. ginseng*. In contrast, each part has unique ginsenosides, and ginsenosides in different parts show obvious structural diversity. It should be emphasized that ginseng aerial parts can regenerate every year, and there is a large amount of rare ginsenosides in stems, leaves, and flower buds. In light of previous research results of the rare ginsenoside bioactivity in red ginseng, it seems that the aerial parts of *P. ginseng* are highly worth developing and utilizing. A conclusion can also be drawn that C17SCV-type ginsenosides and malonyl-ginsenoside are rich in flowers and buds. Therefore, a hypothesis that ginsenosides have physiological roles in ginseng plant development is proposed. The rapid development of high-performance liquid chromatography and mass spectrometry techniques significantly raise the throughput and accuracy of ginsenoside determination.

In the future, (1) with the continuous advancement of detection and identification technology, the analysis method of ginsenosides will develop in the direction of being more sensitive, convenient, and environmentally-friendly, with high-throughput and high-precision. By leveraging these technologies, more monomer compounds will be separated and identified from ginseng, which will develop the knowledge of the diversity of chemical structure of ginsenosides. (2) It is necessary to conduct further research on spatial distribution of ginsenosides in different parts of ginseng, and multidisciplinary collaborations among genomics, proteomics, metabonomics, and transcriptomics could be used to study the physiological functions of ginsenosides. (3) With increasing separation of ginsenosides possessing a complex structure, such as malonyl and C17 side-chain variation, the pharmacological action and pharmacokinetics of these ginsenosides would be further studied to clarify the efficacy of ginseng.

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