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Saponins of ginseng products: a review of their transformation in processing

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The primary processed product of *Panax ginseng* C.A. Meyer (*P. ginseng*) is red ginseng. As technology advances, new products of red ginseng have arisen. Red ginseng products, e.g., traditional red ginseng, sun ginseng, black ginseng, fermented red ginseng, and puffed red ginseng, are commonly used in herbal medicine. Ginsenosides are the major secondary metabolites of *P. ginseng*. The constituents of *P. ginseng* are significantly changed during processing, and several pharmacological activities of red ginseng products are dramatically increased compared to white ginseng. In this paper, we aimed to review the ginsenosides and pharmacological activities of various red ginseng products, the transformation law of ginsenosides in processing, and some clinical trials of red ginseng products. This article will help to highlight the diverse pharmacological properties of red ginseng products and aid in the future development of red ginseng industrialization.

KEYWORDS

red ginseng products, ginsenosides, transformation rule, herbal medicine, pharmacological activities

1 Introduction

Panax ginseng C.A. Meyer (*Panax ginseng*) is an ancient Chinese medicinal material used in Asian nations for over 2,000 years (Kennedy and Scholey, 2003). It has been listed as a medicinal herb in *Shennong Bencao Jing*, a standard Chinese herbal dictionary. *P. ginseng*, *Panax quinquefolius* L., and *P. notoginseng* (Burk) F.H. Chen (*P. notoginseng*), all from the Araliaceae family, are widely used herbs. Several studies over the past few decades have shown that *P. ginseng* and *P. notoginseng* have various pharmacological effects on immunological and neurological system disorders (Liu et al., 2020). The kinds and concentrations of their primary active ingredients, saponins, may

Abbreviations: TRG, Traditional red ginseng; SG, Sun ginseng; BG, Black ginseng; FRG, Fermented red ginseng; PRG, Puffed red ginseng; WG, White ginseng; *P. ginseng* A.C. Meyer, *Panax ginseng*; KRG, Korean red ginseng; TCM, Traditional Chinese medicine; CK, Compound K; PPD, Protopanaxadiol; PPT, Protopanaxatriol; OLE, Oleanane.

be altered throughout the steaming process, and the therapeutic efficacies of raw and steaming *P. ginseng* and *P. notoginseng* vary. These variations in saponins are causally significant (Zhang et al., 2019). Meanwhile, according to traditional Chinese medicine (TCM) theory, their uses differ, since *P. ginseng* strengthens vital energy while *P. notoginseng* encourages blood circulation (Xiong et al., 2022).

P. ginseng is often processed into white ginseng (WG) and traditional red ginseng (TRG), most well-used in clinical applications for their great pharmacological activity. In TCM, the steaming method of *P. ginseng* is initially listed in the Complete Manual of Experience in the Treatment of Sores. The character of TRG is detailed and described in The Ming dynasty's Enlightening Primer of Materia Medica. In steaming processing, the quality of TRG improves with an increase of *P. ginseng* cultivation age. Typically, TRG is produced by six-year-old ginseng in Korea. In addition, the unique and advanced processing technology makes Korean red ginseng (KRG) predominate the world ginseng market. With the development of steaming, fermenting, and puffing technology, many new red ginseng products are being produced, including sun ginseng (SG), black ginseng (BG), fermented red ginseng (FRG), and puffed red ginseng (PRG). These process conditions directly influence the pharmacological activity of red ginseng.

It is widely known ginsenosides can be classified into three types: the protopanaxadiol type (Rb1, Rc, Rb2, and Rd); the protopanaxatriol type (ginsenoside Rg1 and Re); and the oleanolic acid type (ginsenoside Ro and polyacetylene ginsenoside Ro) according to different aglycones (Xu et al., 2014). The various structures of ginsenosides endow them with rich pharmacological activities, such as antioxidation, anti-inflammation, anti-apoptosis, and so on (Choi et al., 2014; Li et al., 2014). Additionally, ginsenosides can be divided into major and rare ginsenosides according to the different content of ginseng, which all have significant pharmacological activities (Wei et al., 2011).

The major ginsenosides occur in WG, TRG, and other new types of red ginseng. In contrast, rare ginsenosides are present in TRG at a trim level, including Rg2, Rg3, Rh1, and Rh2. However, compared with TRG, the rare ginsenosides are abundant in the new types of red ginseng. The types and contents of ginsenosides in different red ginseng products result in various pharmacological activities, and the relationship between ginsenosides and their bioactivities help in the application of red ginseng products in clinical settings.

We aimed to review the relevant clinical studies of red ginseng products and summarize the discovered ginsenoside components of red ginseng. Furthermore, we discuss the structure–functional relationship of ginsenosides. The transformation law of ginsenosides in red ginseng processing are revealed to illustrate the medicinal composition transformation. The other pharmacological activities of red ginseng, such as TRG, SG, BG, FRG, and PRG, are also discussed. We summarize the process and character of the new type of red ginseng, which provides the basis for further research to facilitate the development of red ginseng industrialization in the future.

2 Red ginseng products

2.1 TRG

Generally, TRG is steamed at 90°C–100°C for 2-3 h and then dried (Chung et al., 2014). The large-scale application of TRG began in the Qing Dynasty. According to TCM theory, WG is used to "supply qi and promote the production of body fluids" and enhance physical fitness and disease resistance. In contrast, TRG is often used to "boost yang" and replenishing vital essence with the "warming effect" (Zhang et al., 2012).

During TRG processing, one ginsenoside can be transformed into another by demalonylating, decarboxylating, deglycosylating, and dehydrating (Figure 1). Compared with WG, the rare ginsenosides are the characteristic compound with significant pharmacological activities. TRG exhibits more potent anticancer activity than WG due to the abundance of rare ginsenosides generated from processing (Li et al., 2011; Kim J. H. et al., 2014), which has been further developed into drugs and health products. The pharmacological activity of TRG focuses on anti-aging (Peng et al., 2021), treating erectile dysfunction (Jang et al., 2008), immune-modulating (Kim et al., 2021), the antidepressant effect (Lee et al., 2020), and anti-inflammation (Min et al., 2022). In addition, TRG can inhibit tau aggregation and promote tau dissociation *in vitro*, which can be a potential therapeutic agent to treat neurodegenerative diseases (Shin et al., 2020).

2.2 SG

SG is prepared by steaming fresh ginseng at a temperature of 120°C or higher, which is a higher temperature than during TRG processing (Figure 1). SG contains approximately equal amounts of three major ginsenosides, Rg3, Rg5, and Rk1, in a higher concentration than TRG. One study (Kim et al., 2000) first reported this processed red ginseng, which is more potent in its ability to induce endothelium-dependent relaxation and free radical scavenging activity.

Compared with TRG, SG contains an abundance of ginsenosides Rg3, Rg5, and Rk1 (Kwon et al., 2001). In addition, new acetylated ginsenosides (Rs4, Rs5, Rs6, and Rs7) and dammarane glycosides (Rk1, Rk2, and Rk3) have been isolated from SG (Park et al., 2002a; Park et al., 2002b). These different types and amounts of ginsenosides endow SG with more potent pharmacological effects than TRG under certain pathological conditions. SG reportedly serves several functions, including free radical scavenging (Kang et al., 2006), peroxynitrite scavenging (Kang et al., 2009), antitumor-promoting (Song et al., 2012), antihyperglycemic (Jiao et al., 2014), and cytoprotection activities (Lee C. S. et al., 2012). Moreover, SG has memory-enhancing activities (Lee C. H. et al., 2013), and enhances cognitive function in patients with moderately severe Alzheimer's disease (Heo et al., 2012).

2.3 BG

Due to repeated steaming and drying processes, BG is named according to its surface color change (Figure 1). The nine-time

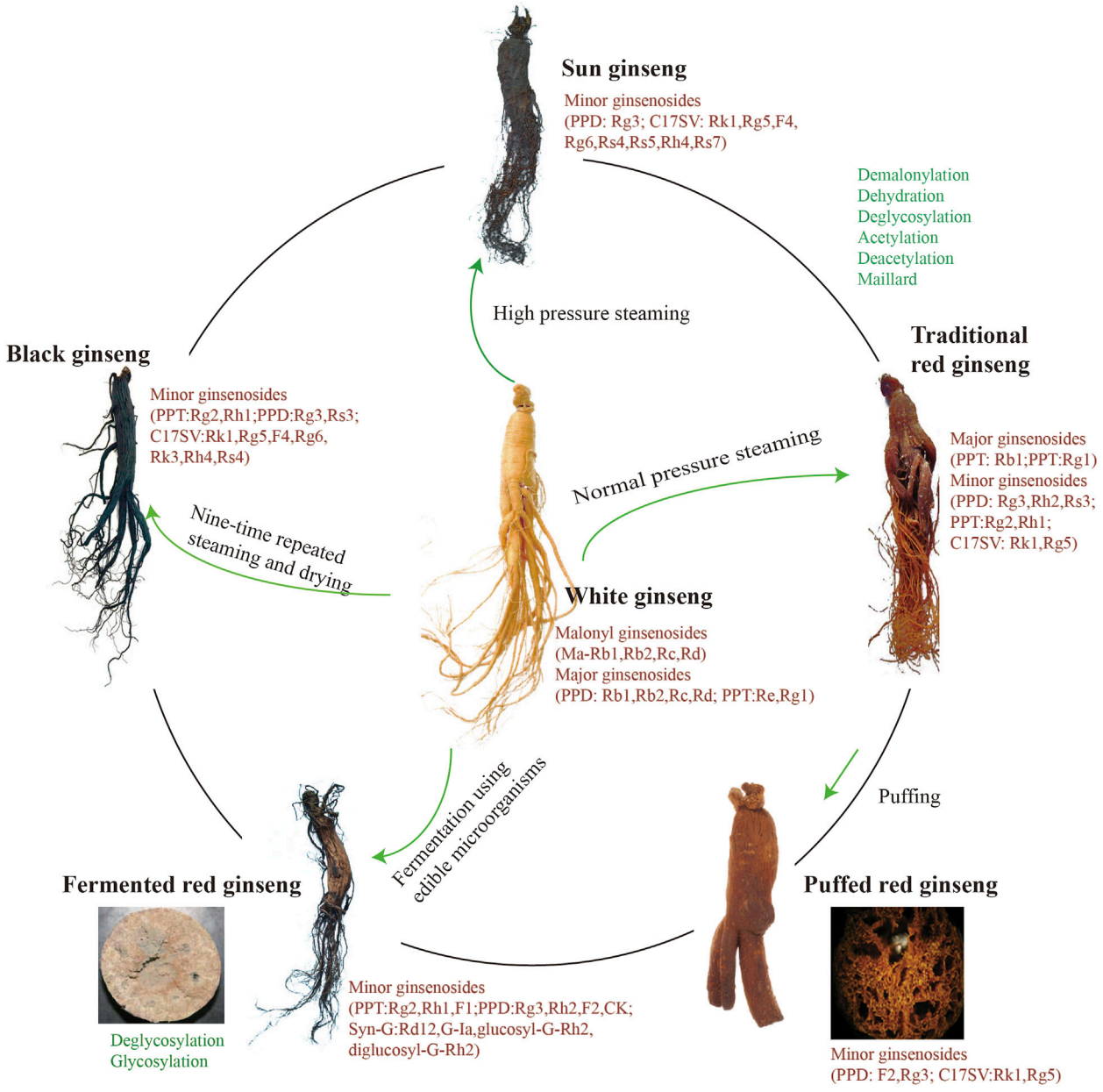

FIGURE 1
Various types of red ginseng.

repeated steaming and drying is a typical method in TCM, mainly to rectify the properties and increase the components of Chinese medicine. Observations indicate that BG improves at temperatures of 95°C or higher, at least from the appearance (Oh et al., 2021). Multiple steaming and drying can enhance the antibacterial activity of BG (Lee H. W. et al., 2021). Compared with the TRG, the total saponins of BG are absorbed faster in the gut and exposed more widely (Yoo et al., 2021). In recent years, this method has been used to manufacture functional food.

After nine repeated steaming cycles, ginseng gradually becomes BG, with increased Rg3 content (Kim, 2015). Nineteen ginsenosides (Rg1, Re, Rf, Rb1, Rc, Rb2, Rd, F4, Rg6, Rk3, Rh4, 20(*S*)-, 20(*R*)-Rg3, 20(*S*)-, 20(*R*)-Rs3, Rk1, Rg5, Rs4, and Rs5) have been determined to be found in BG; among them, the ginsenosides Rg3, Rg5, and Rk1 are the main components (Sun et al., 2009). Research has also revealed that the total ginsenosides increase with number of steam cycles (Lee H. et al., 2012), and that the fructose in BG is 44 times that present in WG and 18.3 times that in RG (Zhu et al., 2019).

In animal and cell culture models, BG plays a role in the prevention and treatment of diseases such as cognitive impairment (Park et al., 2011), obesity (Park et al., 2019), fetal alcohol syndrome (Lee et al., 2009), and breast cancer (Kim and Kim, 2015). BG is a potential anti-aging supplementation, which can reduce the activation of p53-dependent p21 and p16 classical aging pathways in the liver, skeletal muscle, and white fat (Lee S. et al.,

2022). BG can prevent liver injury by resisting oxidative stress, regulating lipid and glucose metabolism, and reducing inflammation and TLR4/NF-κB axis (Jiang et al., 2021; Wei et al., 2022). BG may maintain endothelial integrity by activating Akt, reducing vascular protein leakage, leukocyte infiltration, and proinflammatory factor release in alveolar lavage fluid, and thus plays a protective role against particle-induced lung injury and vascular hyperpermeability (Lee et al., 2019; Kim et al., 2022).

2.4 FRG

Fermenting food through edible microorganisms can produce other active small molecular compounds, which has aroused the interest of most food scientists and dietitians (Oh et al., 2015). Similarly, the fermentation applied in the red ginseng process, which is called FRG, produces a significant change in ginsenoside derivatives and possesses great pharmacological activity (Irfan et al., 2022), such as anti-inflammatory (Kim et al., 2018; Bae et al., 2021), antioxidant (Saba et al., 2018), anti-allergy (Kim et al., 2019), anti-diabetes (Jang et al., 2017), anti-anxiety (Han et al., 2020), and so on. There is another FRG, which involves ginseng steaming, extracting, fermenting, and freeze-drying. The pharmacodynamic function of ginseng after fermentation is improved, which may be related to the increase in ingestion rates and absorption levels of *P. ginseng* (Lee et al., 2015).

Bacteria and fungi, such as *Lactobacillus*, *Bifidobacterium*, *Saccharomyces cerevisiae*, and Red-Koji, mainly perform the fermentation. These microbes are essential in transforming ginseng components (Lee, et al., 2015; Choi et al., 2016). Moreover, mushroom mycelia can provide the microbial environment needed in ginseng fermentation (Bae et al., 2011). Interestingly, fermentation creates a new small molecule, Compound K (CK). CK is transformed from Rb1, Rb2, Rc, and Rd, the metabolite of FRG digested by intestinal microorganisms, and has considerable activity against diabetes, cancer, and immune stimulation (Jung et al., 2019; Kim et al., 2020). In addition, a large amount of Rg3 is fermented into Rh2 by lactic acid bacteria, which have obvious anti-tumor, anti-allergic, and anti-inflammatory activities (Bae et al., 2004; Trinh et al., 2007).

Purple-red ginseng is prepared by fresh ginseng and then through fermentation, steam ripening, and low-temperature ripening. This processing uses bilberry, sugar, and bulgaricus. The ginsenoside, Rg5, is the most abundant ingredient of this FRG. In addition, this FRG might be a beneficial therapeutic supplementary substitute for metabolic syndrome with the efficacy to improve insulin sensitivity and lower postprandial glucose levels (Kho et al., 2016; Lee S. J. et al., 2022).

2.5 PRG

After puffing, the texture of ginseng is loose and porous, and easy to dehydrate. The process goes through rapid heating at atmospheric pressure and immediate pressure reduction, and the product is what we often call PRG (Hoseney, 1986).

The red ginseng was puffed with rice to avoid a burning phenomenon at high temperatures (An et al., 2011). PRG shows higher extraction yield and crude saponin content than non-puffed ginseng (Kim et al., 2008). The primary ginsenosides (Rb1, Rb2, Rc, Rd, Re, and Rg1) are effectively converted into minor ginsenosides (F2, Rg3, Rk1, and Rg5) by puffing, which is similar to the effect of the steaming process on the content of transformed ginsenosides. However, the time required for the transformation of ginsenosides by steaming (4–36 days) is much longer than by puffing (less than 30 min) (Shin et al., 2019). During *in vitro* experiments, the ethanolic extract of PRG shows a more vital antioxidant capacity than TRG. In addition, more robust antioxidant properties are observed in bulk oil and oil-water emulsions (Lee et al., 2018).

3 Ginsenosides in red ginseng and transformation in processing

3.1 Ginsenosides in red ginseng

Ginsenosides are the main active components in red ginseng. So far, about 100 ginsenosides have been discovered in red ginseng (Table 1), and the number is still increasing. In red ginseng products, protopanaxadiol (PPD), protopanaxatriol (PPT), and oleanane (OLE) ginsenosides are the main classification of ginsenosides (Figure 2). Ginsenoside is a triterpenoid saponin with a dammarane skeleton. The ether bond combines carbon-3, carbon-6, or carbon-20 with glycosyl residue. Carbon-20 is a chiral carbon atom presenting the 20(*S*) and 20(*R*) epimers, such as ginsenoside Rg3, Rh2, Rs3, Rg2, and Rh1. Furthermore, dehydration in the carbon-20 can present positional isomers of the double bond at carbon-20 (21) or carbon-20 (22), while the double bond at carbon-20 (22) also presents cis-trans isomers, such as Rg9, F4, Rs6, Rh4, Rs4, Rg5, and Rh3.

The structure of ginsenoside is directly related to anticancer activities. Interestingly, in red ginseng processing, the position of sugar chain hydrolysis (carbon-3 > carbon-6 > carbon-20) results in different degrees of anticancer activity (Kai et al., 2015). The 20(*S*)-ginsenosides have more substantial anticancer potential than their 20(*R*)-stereoisomers (Wang et al., 2007; Seoyoung et al., 2009). Ginsenosides with a double bond at C-20 (21) exhibit more effective anticancer activities than those at C-20 (22) (Kai, et al., 2015).

During red ginseng processing, the polar compounds transform into less polar compounds, which exhibit different pharmacological activity from other red ginseng products. TRG, SG, BG, FRG, and PRG have many ginsenosides in common, such as the major ginsenosides Rb1, Rb2, Rc, Rd, Re, and Rg1. In contrast, the minor ginsenosides are different in content and variety. So, red ginseng product pharmacological activity is significantly different from the diverse ingredients.

3.2 Transformation of ginsenosides

Ginsenosides can cause a structure change during red ginseng processing. Malonyl-ginsenoside is an initial form of ginseng before processing, after which deglycosylation, decarboxylation, and dehydration will occur. For example, Rg2, Rh1, and Rg3 are deglycosylated from Re, Rg1, and Rd; Rg3 and Rg2 are

TABLE 1 Ginsenosides in red ginseng products.

No.	Name	Formula	Plant material	References
1	Acetyl-20(*S*)-ginsenoside Ra1	$C_{60}H_{100}O_{27}$	TRG	Xu et al. (2016)
2	Acetyl-20(*S*)-ginsenoside Ra2	$C_{60}H_{100}O_{27}$	TRG	Xu et al. (2016)
3	20(*S*)-ginsenoside Ra1	$C_{58}H_{98}O_{26}$	TRG	Kasai et al. (1983)
4	20(*S*)-ginsenoside Ra2	$C_{58}H_{98}O_{26}$	TRG	Kasai et al. (1983), Zhou et al. (2016)
5	20(*S*)-ginsenoside Ra3	$C_{59}H_{100}O_{27}$	TRG	Zhou et al. (2016)
6	20(*S*)-ginsenoside Rb1	$C_{54}H_{92}O_{23}$	TRG, BG, FRG, PRG	Xu et al. (2016), Zhou et al. (2016)
7	20(*S*)-ginsenoside Rb2	$C_{53}H_{90}O_{22}$	TRG, BG, FRG, PRG	Xu et al. (2016), Zhou et al. (2016)
8	20(*S*)-ginsenoside Rb3	$C_{53}H_{90}O_{22}$	TRG	Xu et al. (2016), Zhou et al. (2016)
9	20(*S*)-ginsenoside Rc	$C_{53}H_{90}O_{22}$	TRG, BG, FRG, PRG	Xu et al. (2016), Zhou et al. (2016)
10	20(*S*)-ginsenoside Rd	$C_{48}H_{82}O_{18}$	TRG, BG, FRG, PRG	Xu et al. (2016), Zhou et al. (2016)
11	20(*S*)-ginsenoside Rg3	$C_{42}H_{72}O_{13}$	TRG, SG, BG, FRG, PRG	Zhou et al. (2016)
12	20(*R*)-ginsenoside Rg3	$C_{42}H_{72}O_{13}$	TRG, SG, BG, FRG,PRG	Zhou et al. (2016)
13	20(*R*)-ginsenoside Rh2	$C_{36}H_{62}O_{8}$	TRG, FRG	Kitagawa et al. (1983)
14	20(*S*)-ginsenoside Rh2	$C_{36}H_{62}O_{8}$	TRG, FRG	Kitagawa et al. (1983)
15	20(*S*)-ginsenoside Rs1	$C_{55}H_{92}O_{23}$	TRG	Xu et al. (2016), Zhou et al. (2016)
16	20(*S*)-ginsenoside Rs2	$C_{55}H_{92}O_{23}$	TRG	Xu et al. (2016), Zhou et al. (2016)
17	20(*S*)-ginsenoside Rs3	$C_{44}H_{74}O_{14}$	TRG, BG	Baek et al. (1997), Zhou et al. (2016)
18	20(*R*)-ginsenoside Rs3	$C_{44}H_{74}O_{14}$	TRG, BG	Zhou et al. (2016)
19	Malonyl-20(*S*)-ginsenoside Rb1	$C_{57}H_{94}O_{26}$	TRG	Xu et al. (2016)
20	Malonyl-20(*S*)-ginsenoside Rb2	$C_{56}H_{92}O_{25}$	TRG	Xu et al. (2016)
21	Malonyl-20(*S*)-ginsenoside Rd	$C_{51}H_{84}O_{21}$	TRG	Xu et al. (2016)
22	20(*S*)-notoginsenoside R4	$C_{59}H_{100}O_{27}$	TRG	Xu et al. (2016)
23	20(*S*)-pseudo-ginsenoside RC1	$C_{50}H_{84}O_{19}$	TRG	Xu et al. (2016)
24	20(*S*)-quinquenoside R1	$C_{56}H_{94}O_{24}$	TRG	Xu et al. (2016), Zhou et al. (2016)
25	20(*S*)-ginsenoside F2	$C_{42}H_{72}O_{13}$	PRG	An et al. (2011)
26	20(*S*)-ginsenoside Compond-K	$C_{36}H_{62}O_{8}$	FRG	Hasegawa (2004)
27	20(*S*)-notoginsenoside Fa	$C_{59}H_{100}O_{27}$	TRG	Xu et al. (2016)
28	20(*S*)-notoginsenoside Q	$C_{63}H_{106}O_{30}$	TRG	Xu et al. (2016)
29	20(*S*)-notoginsenoside Ra3	$C_{59}H_{100}O_{27}$	TRG	Xu et al. (2016)
30	20(*S*)-notoginsenoside Ra1	$C_{58}H_{98}O_{26}$	TRG	Xu et al. (2016)
31	20(*S*)-notoginsenoside Ra2	$C_{58}H_{98}O_{26}$	TRG	Xu et al. (2016)
32	20(*S*)-notoginsenoside Fc	$C_{58}H_{98}O_{26}$	TRG	Xu et al. (2016)

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TABLE 1 (*Continued*) Ginsenosides in red ginseng products.

No.	Name	Formula	Plant material	References
33	20(*S*)-quinquenoside III	$C_{51}H_{86}O_{21}$	TRG	Xu et al. (2016)
34	20(*S*)-ginsenoside Re	$C_{48}H_{82}O_{18}$	TRG, BG, PRG	Xu et al. (2016), Zhou et al. (2016)
35	Acetyl-20(*S*)-ginsenoside Re	$C_{50}H_{84}O_{19}$	TRG	Xie et al. (2012)
36	20(*S*)-ginsenoside Re2	$C_{48}H_{82}O_{19}$	TRG	Zhou et al. (2016)
37	Acetyl-20(*S*)-ginsenoside Rf	$C_{44}H_{74}O_{15}$	TRG	Xu et al. (2016)
38	20(*S*)-ginsenoside Rf	$C_{42}H_{72}O_{14}$	TRG, BG	Zhou et al. (2016)
39	20(*R*)-ginsenoside Rf	$C_{42}H_{72}O_{14}$	TRG	Lee et al. (2013a), Zhou et al. (2016)
40	20(*S*)-ginsenoside Rf-1a	$C_{42}H_{72}O_{14}$	TRG	Zhou and Yang (2015), Zhou et al. (2016)
41	Acetyl-20(*S*)-ginsenoside Rg1	$C_{44}H_{74}O_{15}$	TRG	Xu et al. (2016)
42	20(*S*)-ginsenoside Rg1	$C_{42}H_{72}O_{14}$	TRG, BG, PRG	Zhou et al. (2016)
43	20(*S*)-ginsenoside Rg2	$C_{42}H_{72}O_{13}$	TRG	Zhou et al. (2016)
44	20(*R*)-ginsenoside Rg2	$C_{42}H_{72}O_{13}$	TRG	Zhou et al. (2016)
45	20-gluco-20(*S*)-ginsenoside Rf	$C_{48}H_{82}O_{19}$	TRG	Zhou et al. (2016)
46	20(*S*)-ginsenoside Rh1	$C_{36}H_{62}O_{9}$	TRG	Xu et al. (2016), Zhou et al. (2016)
47	20(*R*)-ginsenoside Rh1	$C_{36}H_{62}O_{9}$	TRG	Xu et al. (2016), Zhou et al. (2016)
48	20(*S*)-notoginsenoside R1	$C_{47}H_{80}O_{18}$	TRG	Xu et al. (2016), Zhou et al. (2016)
49	20(*S*)-notoginsenoside R2	$C_{44}H_{74}O_{15}$	TRG	Zhou et al. (2016)
50	20(*R*)-notoginsenoside R2	$C_{44}H_{74}O_{15}$	TRG	Zhou et al. (2016)
51	3β,12β-dihydroxydammar-20 (22) E, 24-diene-6-O-β-D-xylopyranosyl-(1→2)-O-β-D-glucopyranoside	$C_{41}H_{68}O_{12}$	TRG	Zhou et al. (2016)
52	12-O-glucoginsenoside Rh4	$C_{42}H_{70}O_{13}$	SG	Cho et al. (2013)
53	20 (22) Z-ginsenoside Rh4	$C_{36}H_{60}O_{8}$	TRG, SG, BG	Zhou et al. (2016)
	20 (22) E-ginsenoside Rh4	$C_{36}H_{60}O_{8}$	TRG, SG, BG	Baek et al. (1996), Zhou et al. (2016)
54	12β,25-dihydroxydammar-20 (22) E-ene-3-O-β-D-glucopyranosyl-(1→2)-O-β-D-glucopyranoside	$C_{42}H_{72}O_{14}$	TRG	Zhou et al. (2016)
55	20 (22) E-ginsenoside Rg11	$C_{42}H_{70}O_{15}$	SG	Cho et al. (2013)
56	23-O-methylginsenoside Rg11	$C_{43}H_{72}O_{15}$	TRG	Zhou and Yang, (2015); Zhou et al. (2016)
57	20 (22) E-ginsenoside Rh10	$C_{36}H_{62}O_{9}$	SG	Cho et al. (2013)
58	20 (22) E-ginsenoside F4	$C_{42}H_{70}O_{12}$	TRG, BG	Ryu et al. (1996), Zhou et al. (2016)
59	20 (22) Z-ginsenoside F4	$C_{42}H_{70}O_{12}$	TRG, BG	Zhou et al. (2016)
60	Ginsenoside Rf2	$C_{42}H_{70}O_{14}$	TRG	Park et al. (1998)
61	Ginsenoside Rg5	$C_{42}H_{70}O_{12}$	TRG, SG, BG, FRG, PRG	Xu et al. (2016), Zhou et al. (2016)
62	Ginsenoside Rz1	$C_{42}H_{70}O_{12}$	TRG, SG	Zhou et al. (2016)
63	Ginsenoside Rg6	$C_{42}H_{70}O_{12}$	TRG, BG	Zhou et al. (2016)

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TABLE 1 (*Continued*) Ginsenosides in red ginseng products.

No.	Name	Formula	Plant material	References
64	Ginsenoside Rk1	$C_{42}H_{70}O_{12}$	SG, TRG, BG, PRG	Zhou et al. (2016)
65	Ginsenoside Rk2	$C_{42}H_{60}O_{7}$	SG	Park et al. (2002a)
66	Ginsenoside Rk3	$C_{42}H_{60}O_{8}$	SG, TRG, BG	Park et al. (2002b); Zhou et al. (2016)
67	20 (22) E-ginsenoside Rs4	$C_{44}H_{72}O_{13}$	SG, BG	Park et al. (2002a)
68	20 (22) Z-ginsenoside Rs4	$C_{44}H_{72}O_{13}$	TRG, SG, BG	Zhou and Yang, (2015); Zhou et al. (2016)
69	Ginsenoside Rs5	$C_{44}H_{72}O_{13}$	SG, BG	Park et al. (2002b)
70	Ginsenoside Rs6	$C_{38}H_{62}O_{9}$	SG	Park et al. (2002a)
71	Ginsenoside Rs7	$C_{38}H_{62}O_{9}$	SG	Park et al. (2002b)
72	20 (22) Z-ginsenside Rg9	$C_{42}H_{70}O_{13}$	TRG	Lee et al. (2013b)
73	20 (22) E-ginsenside Rg9	$C_{42}H_{70}O_{13}$	TRG	Lee et al. (2013a); Zhou et al. (2016)
74	Ginsenside Rg10 (8)	$C_{42}H_{70}O_{13}$	TRG	Lee et al. (2013b)
75	Ginsenoside Rg4	$C_{42}H_{70}O_{12}$	TRG	Xu et al. (2018)
76	20 (22) Z-ginsenoside Rh3	$C_{36}H_{60}O_{7}$	TRG	Kim et al. (1996)
77	Ginsenoside Ro	$C_{48}H_{76}O_{19}$	TRG	Zhou et al. (2016)
78	Ginsenoside Ro methyl ester	$C_{49}H_{78}O_{19}$	TRG	Zhou et al. (2016)
79	Polyacetyleneginsenoside Ro	$C_{65}H_{100}O_{21}$	TRG	Zhou et al. (2016)
80	Ginsenoside-Ro-6′-butyl ester	$C_{52}H_{84}O_{19}$	TRG	Zhou and Yang (2015); Zhou et al. (2016)
81	Chikusetsusaponin IVa methyl ester	$C_{43}H_{68}O_{14}$	TRG	Zhou et al. (2016)
82	Chikusetsusaponin IVa butyl ester	$C_{46}H_{74}O_{14}$	TRG	Zhou et al. (2016)
83	Zingibroside R1-6′-butyl ester	$C_{46}H_{74}O_{14}$	TRG	Zhou et al. (2016)
84	Zingibroside R1-6′-methyl ester	$C_{43}H_{68}O_{14}$	TRG	Zhou et al. (2016)
85	Oleanolic acid- 28-Oleanolic acid- 28-O- beta- D- Glucopyranoside	$C_{36}H_{58}O_{8}$	TRG	Xu et al. (2016)
86	20(*S*),25(*R*)-epoxydammarane- 3b,12b,24b,26-tetraol	$C_{30}H_{52}O_{5}$	TRG	Zheng et al. (2016)
87	20(*S*),25-epoxydammarane-3b,12b,24a-triol	$C_{30}H_{52}O_{4}$	TRG	Zheng et al. (2016)
88	Stipuleanoside R1	$C_{47}H_{74}O_{18}$	TRG	Xu et al. (2016)
89	Cynarasaponin C	$C_{35}H_{70}O_{19}$	TRG	Xu et al. (2016)
90	Spinasaponin A	$C_{35}H_{70}O_{19}$	TRG	Xu et al. (2016)
91	Quadrangulcoside	$C_{54}H_{90}O_{23}$	TRG	Xu et al. (2016)
92	Melilotoside	$C_{41}H_{68}O_{12}$	TRG	Xu et al. (2016)
93	Hebevinoside VI	$C_{41}H_{68}O_{12}$	TRG	Xu et al. (2016)
94	Quinquenoside F1	$C_{42}H_{74}O_{15}$	TRG	Xu et al. (2016)
95	Ursan-3b,19a,22b-triol-3-O-b-D-glucopyranosyl (2'→1″)-b-D-glucopyranoside	$C_{42}H_{72}O_{13}$	TRG	Chung et al. (2014)
96	Ursan-3a,11b-diol-3-O-a-D-glucopyranosyl-(6'→1″)-a-D-glucopyranosyl-(6"→1‴)-a-D-glucopyranosyl-(6‴→1⁗)-a-D-glucopyranoside	$C_{54}H_{92}O_{22}$	TRG	Chung et al. (2014)
97	Lanost-5,24-dien-3b-ol-3-O-b-D-glucopyranosyl-(6'→1″)-b-D-glucopyranosyl-(6"→1‴)-b-D-glucopyranoside	$C_{48}H_{80}O_{16}$	TRG	Chung et al. (2014)

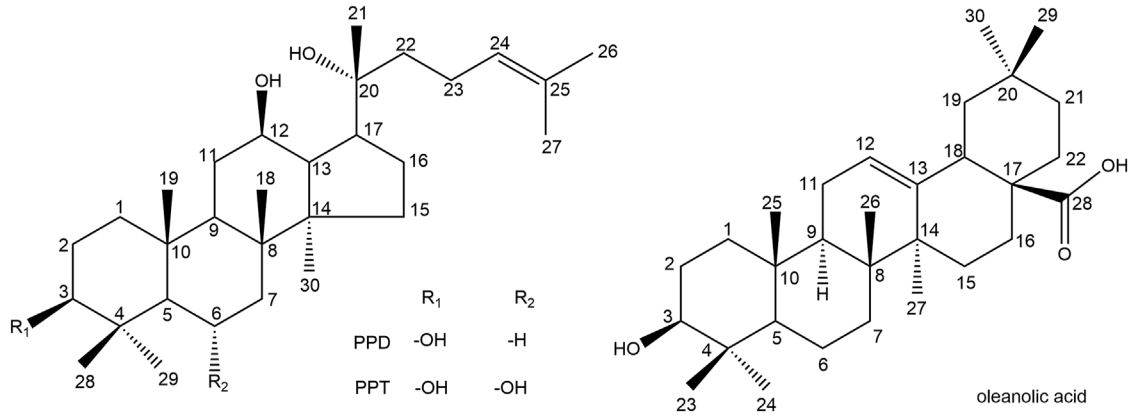

FIGURE 2
Structure of protopanaxadiol (PPD), protopanaxatriol (PPT), and oleanolic acid (OA).

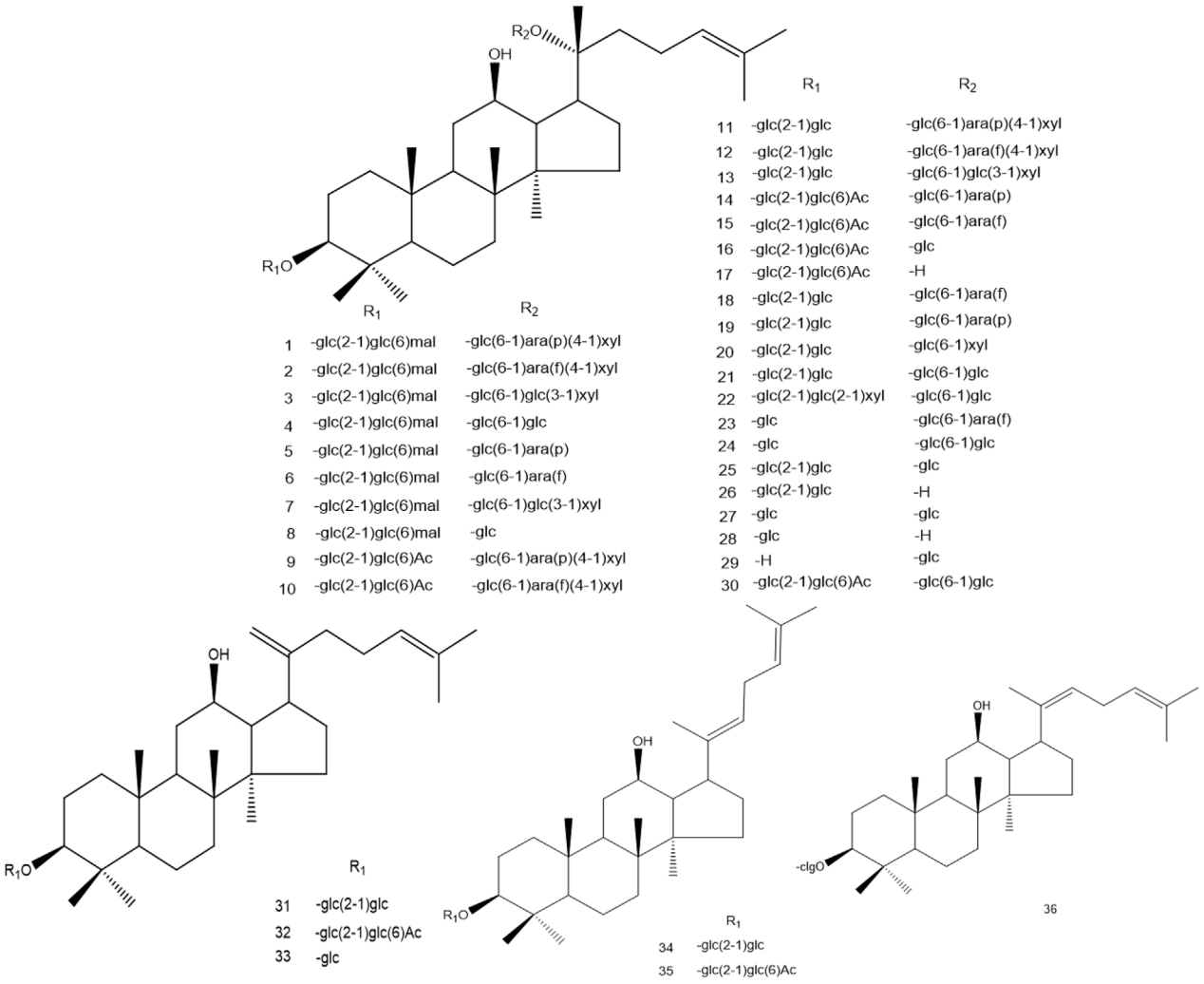

FIGURE 3
Structure of protopanaxadiol ginsenosides. (ara(f):α-*L*-arabinofuranosyl; ara(p):α-*L*-arabinopyranosyl; rha:α-*L*-ahamnopyranosyl; glc:β-*D*-glucopyranosyl; xyl:β-*D*-xylopyranosyl; mal:malonyl; Ac:acetyl).

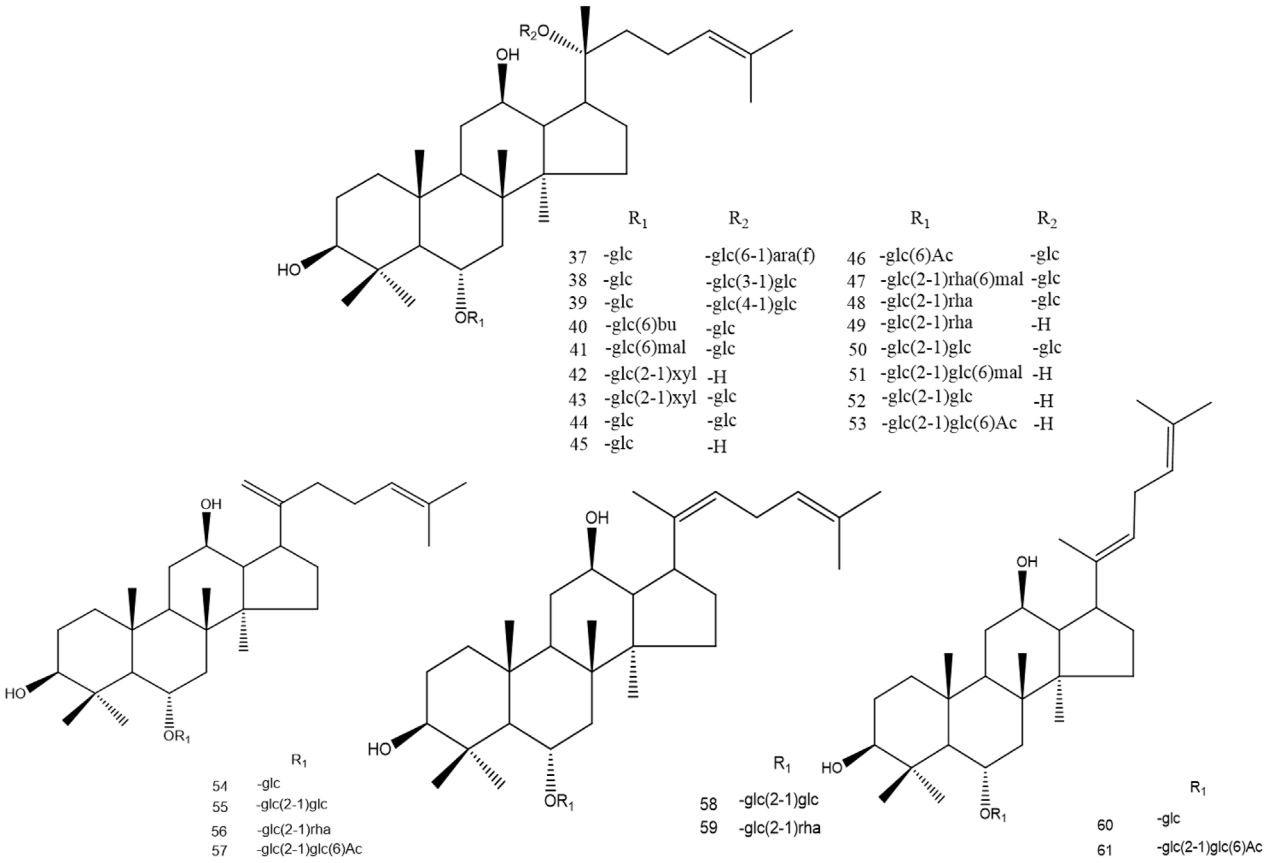

FIGURE 4
Structure of protopanaxatriol ginsenosides. (ara(f):α-*L*-arabinofuranosyl; rha:α-*L*-ahamnopyranosyl; glc:β-*D*-glucopyranosyl; xyl:β-*D*-xylopyranosyl; mal:malonyl; bu:butyl; Ac:acetyl).

dehydrated to form Rg5 and Rg6; and malonyl-ginsenoside Rb2 and Rc are decarboxylated to create Rs1 and Rs2 (Chen et al., 2020). Previous research has indicated that ginsenoside Rb1 and Rb2 can transform into ginsenoside Rg3, and ginsenoside Re can transform into ginsenoside Rg2 (Lee et al., 2008; Kim Y. J. et al., 2014). The Maillard reaction is also the primary chemical reaction in red ginseng processing, whereby products are generated whenever reducing sugars are heated with amino acids, peptides, or proteins (Chen and Kitts, 2012). These products are a significant source of compounds that enhance antioxidant activity through heat treatment (Chen and Kitts, 2011). In the Maillard reaction, ginsenosides provide the reducing sugars and then transform into other ginsenosides (Yamabe et al., 2013).

Before being processed into red ginseng, malonyl-20(*S*)-ginsenoside is a natural compound of ginseng. The deglycosylate in carbon-20 easily occurs after processing; however, the location of the 20(*S*) and 20(*R*) epimers remains to be determined. The 20(*R*)-ginsenosides are present through the OH group selective attack after the glycosyl residue elimination at carbon-20 during red ginseng processing (Kang et al., 2007). For example, the ginsenoside Rg3, Rh2, Rs3, Rg2, Rh1, and Rf both have the 20(*S*) and 20(*R*) epimers.

TRG processing is mainly conducted by decarbonylation, decarboxylation, and the first deglycosylation in carbon-20 of the dammarane skeleton. SG, BG, and PRG promote these reactions. The second deglycosylation is mainly conducted in carbon-20 of the dammarane skeleton and dehydration in this position. However, the FRG processes some characteristic ginsenosides, such as ginsenoside CK, for microbial metabolism. At the same time, the amount of some minor ginsenosides, such as ginsenoside Rh2, Rg1, and Rh1, also increase with the fermentation process. The conversion pathway of oleanane ginsenosides is similar to dammarane ginsenosides. The demethylation, debutylization, and deglycosylation of ester bonds can easily occur at carbon-3 and carbon-28. The ether bond is stable at carbon-3 in the oleanane skeleton, which is also stable between sugars in this position (Figures 3–6).

4 20(*R*)- and 20(*S*)-ginsenoside isomerism

Ginsenosides, active ingredients of *P. ginseng*, like 20(*R*)-ginsenoside and 20(*S*)-ginsenoside, exist as stereoisomers depending on the position of the hydroxyl group on carbon-20. A literature survey shows that ginsenoside Rg3 and Rh2 are stereospecific in the stimulation of the pharmacological activity. 20 (*S*)-ginsenoside is the dominant conformation relative to 20(*R*)-ginsenoside in terms of some activity experiments.

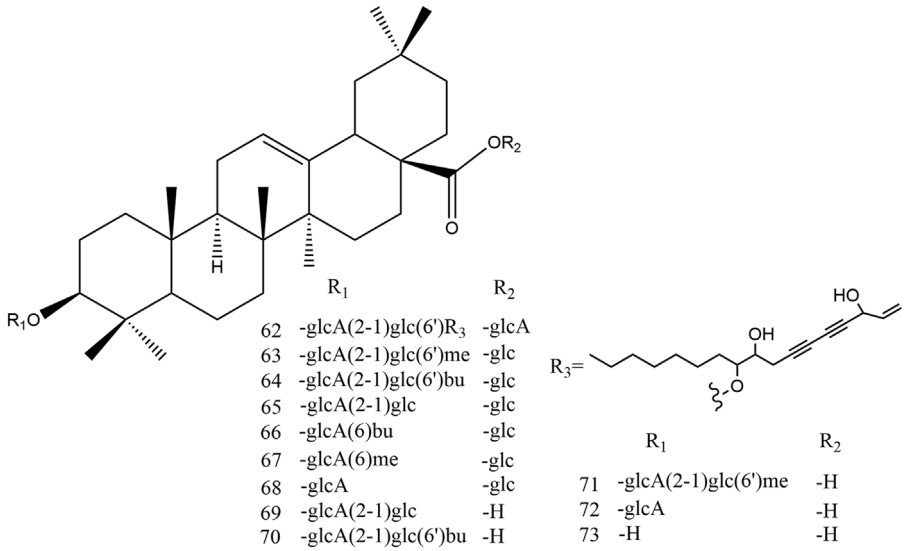

FIGURE 5
Structure of oleanolic acid ginsenosides. (glcA: *β-D*-glucuronosyl; glc: *β-D*-glucopyranosyl; me: methyl; bu: butyl).

In an *in vitro* study, the stereochemistry of the hydroxyl group at C-20 may play an important role in preventing rotavirus infection, and anticancer and osteoclastogenesis inhibitory activity. Ginsenoside Rb2 and its hydrolytic product; 20(*S*)-ginsenoside Rg3, but not 20(*R*)-ginsenoside Rg3, prevent rotavirus infection (Yang et al., 2018). The regulation of DNA methylation may play an important role in the inhibitory effect of ginsenoside Rg3 on the growth of the HepG2 cell line. The inhibitory effect of 20(*S*)-ginsenoside Rg3 is stronger than that of 20(*R*)-ginsenoside Rg3 (Teng et al., 2017). 20(*S*)-Ginsenoside Rh2 potently protects HepG2 cells cytotoxicity treated with tert-butyl hydroperoxide, but 20(*S*)-ginsenoside Rg3 weakly protects it (Lee et al., 2005). The ginsenoside 20(*R*)-ginsenoside Rh2, but not ginsenoside 20(*S*)-ginsenoside Rh2, shows selective osteoclastogenesis inhibitory activity without any cytotoxicity on osteoclastogenesis using RAW264 cells (Liu et al., 2009).

During *in vivo* experiments, ginsenoside isomers showed significant differences in improving immunity, survival ability, and alleviating diabetes symptoms. 20(*R*)- ginsenoside Rg3 has a more potent adjuvant activity of the immune response than 20(*S*)-ginsenoside Rg3 with highly upregulated serum IFN-γ and IL-5 (Wei et al., 2012). The novel characteristics of 20(*S*)-ginsenoside Rg3 exhibited higher pharmacological effects in insulin secretion and AMPK activation than 20(*R*)-ginsenoside Rg3, suggesting that ginsenoside Rg3 epimers show differential activities; 20(*S*)-ginsenoside Rg3 may be a valuable candidate for an anti-diabetic agent (Park et al., 2008). 20(*S*)-ginsenoside Rg3 promotes angiogenesis by activating the AKT/ERK-eNOS signal pathway, and its activity is significantly more potent than that of 20(*R*)-ginsenoside Rg3 (Kwok et al., 2012). In addition, ginsenosides can also maintain body growth with a supplement of 20(*S*)-, but not 20(*R*)-ginsenoside Rg3 in a cholesterol-deprived medium (Lee et al., 2011).

The hydroxyl stereochemistry at C-20 has a great influence on the activity of ginsenosides. In the production process, the processing method of red ginseng should be changed according to the actual demand to achieve the maximum transformation of the target ginsenosides. For example, under optimum reaction conditions, the actual 20(*R*)-ginsenoside Rg3 converts PPD ginsenosides (Sun et al., 2013). As mentioned, ginsenoside Rg3, Rh2, Rs3, Rg2, Rh1, and Rf have the 20(*S*) and 20(*R*) epimers. There are few studies regarding the structure-activity relationship of other ginsenosides, which is still an urgent problem to be solved. In the future, these problems should be explored to determine the greater value of red ginseng.

5 Clinical trials of red ginseng

ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted worldwide. Through the ClinicalTrials.gov platform (https://clinicaltrials.gov/), a search of the term "red ginseng" found 78 research projects; while the exclusion of all other forms of ginseng other than red ginseng obtained 39 clinical studies (Figure 7); only six of these research projects were successfully concluded and the results were reported. These results suggest that KRG is efficacious as an adjuvant treatment for patients experiencing residual symptoms of major depression (Jeong et al., 2015), reducing proinflammatory cytokines and fatigue in overweight patients with non-alcoholic fatty liver disease (Hong et al., 2016), and protecting subjects from contracting acute respiratory illness (Lee S. A. et al., 2012). KRG may have beneficial effects for dry mouth in women, especially in those of menopausal age, but not in men (Park et al., 2010). There is no evidence that KRG has an effect on blood pressure, fasting blood glucose, or arterial stiffness in subjects with metabolic syndrome (Park et al., 2012). Based on mostly low certainty evidence, ginseng

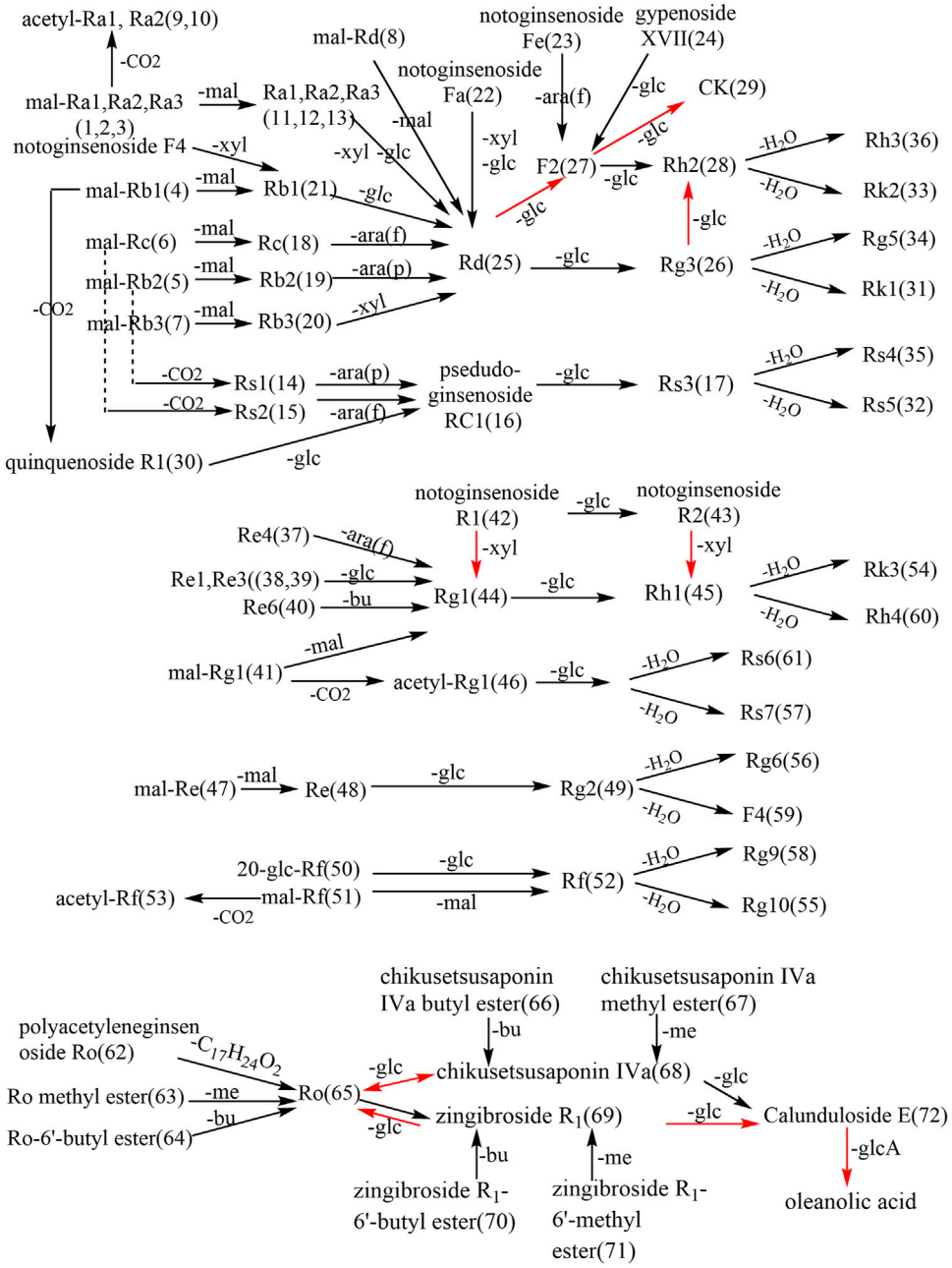

FIGURE 6
Transformation of ginsenosides in red ginseng products. (ara(f):*α-L*-arabinofuranosyl; ara(p):*α-L*-arabinopyranosyl; rha:*α-L*-ahamnopyranosyl; glc: *β-D*-glucopyranosyl; glcA: *β-D*-glucuronosyl; xyl:*β-D*-xylopyranosyl; mal:malonyl; bu: butyl. The red arrow represents biotransformation).

may only have trivial effects on erectile function or satisfaction with intercourse compared to a placebo when assessed using validated instruments (Lee Y. S. et al., 2021). South Korea and Canada lead the studies. Twenty-eight institutions from seven countries participated, including the Clinical Trial Center for Functional Foods Chonbuk National University Hospital, Clinical Nutrition and Risk Factor Modification Centre, and Clinical Trial Center for Functional Foods. Red ginseng is mainly used as a dietary supplement, and a small part is used in drug research. There are 31 research directions, primarily focusing on diabetes mellitus type 2, health, hypertension, and blood pressure, etc. Given this, clinical studies of red ginseng mainly focus on Korea and Canada and the use of dietary supplements in human clinical studies of type II diabetes, health, hypertension, and other neurological diseases.

6 Discussion

Red ginseng products derived from fresh ginseng include TRG, SG, BG, FRG, and PRG. Their chemical compositions are similar

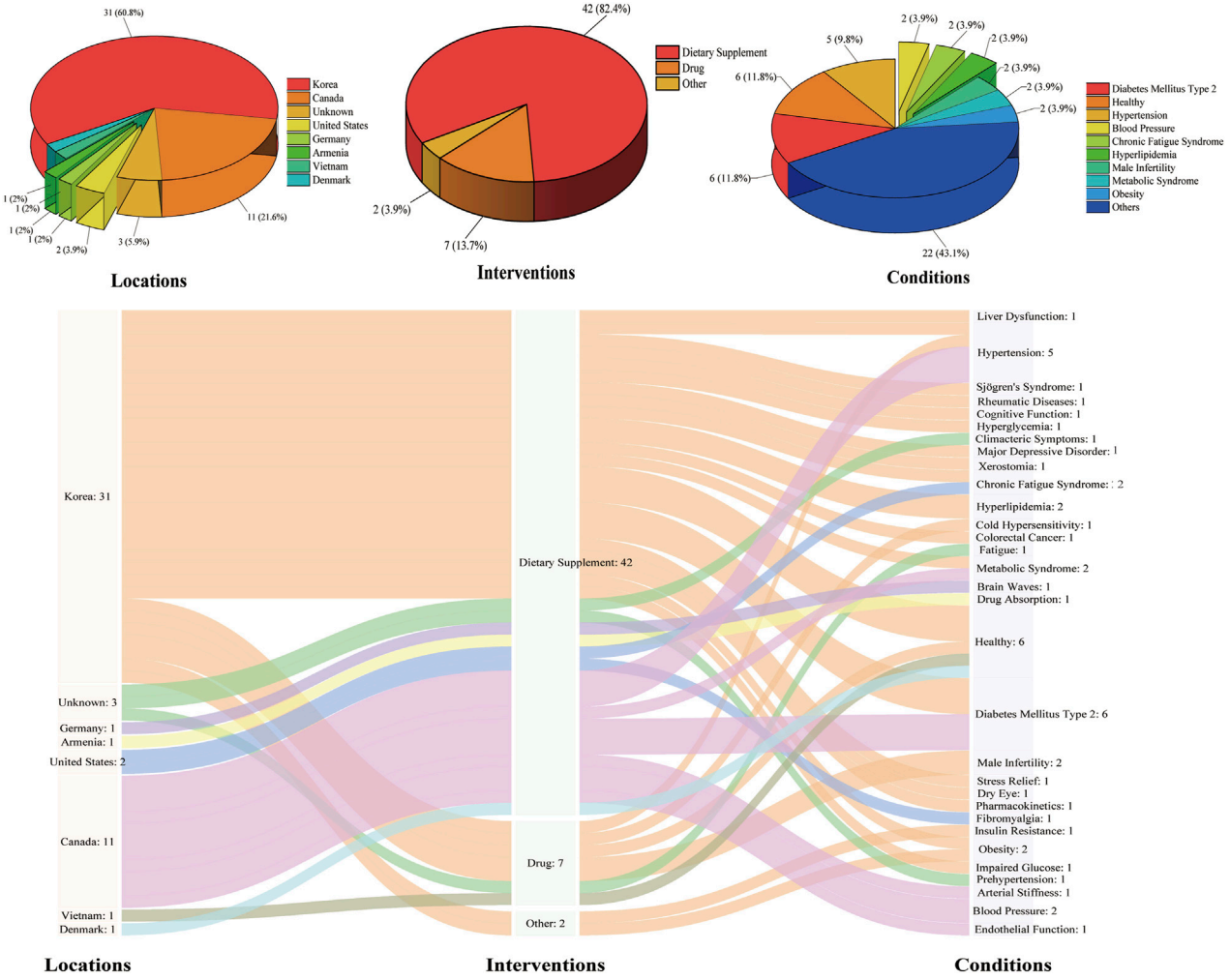

FIGURE 7
Analysis of clinical trials of red ginseng.

because all of them were derived from the same original plant, *P. ginseng*. The chemical composition of these products has been extensively reported. However, the research mainly focuses on TRG. The chemical composition differences between other red ginseng products remain undiscovered. Interestingly, the transformation law of ginsenosides in different red ginseng processing is similar. Some identical rare ginsenosides make other red ginseng products with similar pharmacological activities. For example, ginsenosides (Rg3, Rg5, and Rk1) of SG have been reported to improve cognitive function; ginsenosides (Rg3, Rg5, and Rk1) of BG are the same as SG, and many studies have been conducted on the prevention and treatment of obesity, breast cancer, cognitive impairment, and fetal a syndrome, etc. The composition of FRG by microorganisms is similar to that of other red ginseng products, which convert normal ginsenosides into minor ginsenosides and produce a unique component CK, which is mainly used in improving allergies, diabetes, anxiety, and other aspects, and may play an essential role in metabolic syndrome and other elements. PRG significantly reduces the conversion time of normal ginsenosides into minor ginsenosides. According to current *in vitro* studies, the anticancer effects of PRG are worthy of further studies.

Unfortunately, chemical constituents and efficacy studies on red ginseng products are still lacking, especially for PRG. The pharmacological activities focus on TRG and another new type of red ginseng. In some pharmacological activities, the new kind of red ginseng is more vital than TRG. There is little systematic research comparing the differences in pharmacological activities between the new types of red ginseng, and further studies should be conducted on the mechanism of pharmacodynamics in different red ginseng products applied appropriately in the clinic.

During red ginseng processing, the polar compounds are transformed into less polar compounds; demalonylation and decarboxylation easily occur, and the malonyl-ginsenosides decarboxylate into acetyl-ginsenosides; the Maillard reaction is also a reaction in red ginseng processing (Figure 1). The different process influences the content and variety of minor ginsenosides. Usually, the ginsenoside transformation of the new type of red ginseng is more vital than TRG. So, the amount of minor ginsenosides is minimal in TRG but abundant in the new type of

red ginseng. With a further understanding of the structure and efficacy of ginsenosides, rare ginsenosides, such as Rg3 and Rh2, have been found to have significant pharmacological activities. The species and proportion of ginsenosides are different during red ginseng processing, which suggests that processing is crucial for the efficacy of red ginseng products. The processing of TCM expands the scope of the application thereof, which is the charm of TCM.

7 Conclusion

Modern technology applied to red ginseng processing provides further specifications. At the same time, modern technology can adapt to determine the development law of modern diseases. Red ginseng products are used in the treatment of AD, diabetes, and other conditions, and further systematic comparative studies of the chemical composition can promote full utilization thereof. The types and proportions of rare ginsenosides require further in-depth comparative analyses in pharmacological activity for better selection of drugs according to different clinical needs. Many researchers are focused on red ginseng processing, especially with regards the steam method and the detailed parameters of processing. In contrast, FRG has the advantage of microbial transformation in the ginsenosides to enhance the amount and variety of minor ginsenosides. To accurately control the processing conditions of different red ginseng products, we can maintain the transformation of ginsenosides and produce red ginseng products for specific diseases. This difference in ginsenosides results in red ginseng products being selectively applied in the clinic.

The processing of red ginseng can be developed in the direction of accurate processing and precise treatment. Moreover, ginsenoside transformation of red ginseng and the structure–functional relationship of ginsenoside derivatives can illustrate the medicinal compositions of this different pharmacological activity, which make the application of red ginseng practical and facilitate the development of new types of red ginseng in the future.

Author contributions

X-FX and X-RL developed a major research plan. JW, C-SL, and XW analyze data. S-QC, and H-XZ draw charts. X-WY write manuscripts. QL and H-MR helped collect data and references. X-XW and L-JX implemented corrections in the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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