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Review paper

Ginsenoside Rc: A potential intervention agent for metabolic syndrome

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ABSTRACT

Ginsenoside Rc, a dammarane-type tetracyclic triterpenoid saponin primarily derived from *Panax ginseng*, has garnered significant attention due to its diverse pharmacological properties. This review outlined the sources, putative biosynthetic pathways, extraction, and quantification techniques, as well as the pharmacokinetic properties of ginsenoside Rc. Furthermore, this study explored the pharmacological effects of ginsenoside Rc against metabolic syndrome (MetS) across various phenotypes including obesity, diabetes, atherosclerosis, non-alcoholic fatty liver disease, and osteoarthritis. It also highlighted the impact of ginsenoside Rc on multiple associated signaling molecules. In conclusion, the anti-MetS effect of ginsenoside Rc is characterized by its influence on multiple organs, multiple targets, and multiple ways. Although clinical investigations regarding the effects of ginsenoside Rc on MetS are limited, its proven safety and tolerability suggest its potential as an effective treatment option.

1. Introduction

Metabolic syndrome (MetS) comprises a collection of clinical syndromes characterized by a combination of central obesity, dyslipidemia, impaired glucose metabolism, and hypertension [1]. It affects approximately 25% of the global population [2], with a prevalence of around 31% among Chinese adults [3] and reaching up to 41% in men and 38% in women in Europe [4]. Alarmingly, the prevalence of MetS has been steadily increasing over time [5,6], imposing a substantial burden on global health. Moreover, MetS significantly elevates the risk of cardiovascular disease, non-alcoholic fatty liver disease (NAFLD), chronic kidney disease, osteoarthritis (OA), neurodegenerative diseases, and various cancers [7,8]. To mitigate the impact of MetS on global health and longevity, it is crucial to discover novel treatments that are both safe and effective. Drawing inspiration from the traditional medicine practices of several East Asian countries, extensive researches have focused on investigating the anti-MetS properties of ginseng, a critical "medicine food homologous" herb, and its bioactive compounds [9–11].

Ginsenosides are the primary active constituents of ginseng, exerting notable pharmacological effects [12]. Based on their abundance in the source plant, ginsenosides can be categorized as major ginsenosides and rare ginsenosides, with major ginsenosides comprising over 90% of the total saponin content [13]. Among the major ginsenosides, Ginsenoside Rc (PubChem CID: 12855889) stands out. It is a protopanaxadiol type tetracyclic triterpenoid saponin of the dammarane-type. This paper conducted an extensive search across major databases, including PubMed, ScienceDirect, SpringerLink, China National Knowledge Infrastructure, Web of Science, and GeenMedical. With "ginsenoside Rc" and "obesity", "diabetes", "atherosclerosis", "non-alcoholic fatty liver disease", or "osteoarthritis" as keywords, all the reports closely related to metabolic syndrome in the past 40 years were extensively extracted and analyzed to form a literature review. This review encompasses the physicochemical properties, sources, biosynthetic pathways, extraction and quantification methods, and pharmacokinetic characteristics of ginsenoside Rc. Moreover, it

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provides an in-depth examination of its biological effects against MetS and the underlying mechanisms. Additionally, a thorough analysis of its safety is conducted, laying the groundwork for the potential clinical utilization of ginsenoside Rc.

2. Physicochemical properties, sources, and putative biosynthetic pathways of ginsenoside Rc

Ginsenoside Rc is a dammarane-type ginsenoside substituted by hydroxy groups at the 3beta, 12beta, and 20 pro-S positions. The hydroxy groups at positions 3 and 20 have been converted to beta-D-glucopyranosyl-(1→2)-beta-D-glucopyranoside and alpha-L-arabinofuranosyl-(1→6)-beta-D-glucopyranoside, respectively. Simultaneously, a double bond has been introduced at the 24–25 position. It has a molecular formula of $C_{53}H_{90}O_{22}$ and a chemical structure shown in Fig. 1. Ginsenoside Rc appears as a white powder with a relative molecular mass of 1079.27 g/mol, a melting point of 199–201 °C, a boiling point of 1128.3 ± 65.0 °C (at 101.3 kPa), a density of 1.42 ± 0.1 g/cm^3, an acidity coefficient of 12.85 ± 0.70, and a flash point of 636.2 ± 34.3 °C. It is soluble in water, methanol, and ethanol but insoluble in ether and benzene. Ginsenoside Rc is primarily derived from ginseng, American *ginseng*, *Panax notoginseng*, and *Panax japonicus*, which are araliaceous plants known as medicine food homologs. Its distribution in these source plants exhibits tissue-specific patterns [14,15]. For instance, in ginseng, ginsenoside Rc is predominantly found in rhizomes, roots, stems, leaves, flower buds, and fruits [16], with its content generally increasing with prolonged growth time [17]. In *Panax notoginseng*, ginsenoside Rc is present in stems, leaves, flowers, and fruit stalks [15,18,19]. Additionally, ginsenoside Rc is present in the rhizomes, main roots, and lateral roots of American ginseng and *Panax japonicus* [20,21].

The biosynthesis of ginsenoside Rc involves a series of processes, including the biosynthesis of terpene precursors, the formation of triterpene backbone, and the generation of ginsenosides [22–25] (Fig. 1). Initially, two types of terpene precursors, isopentenyl diphosphate (IPP) and its isomer dimethylallyl pyrophosphate (DMAPP), are produced through the mevalonic acid pathway and the 2-C-methyl-D-erythritol-4-phosphate pathway [26–29]. Isopentenyl diphosphate isomerase catalyzes the reversible conversion of IPP and DMAPP. The nucleophilic reagent IPP readily condenses with the

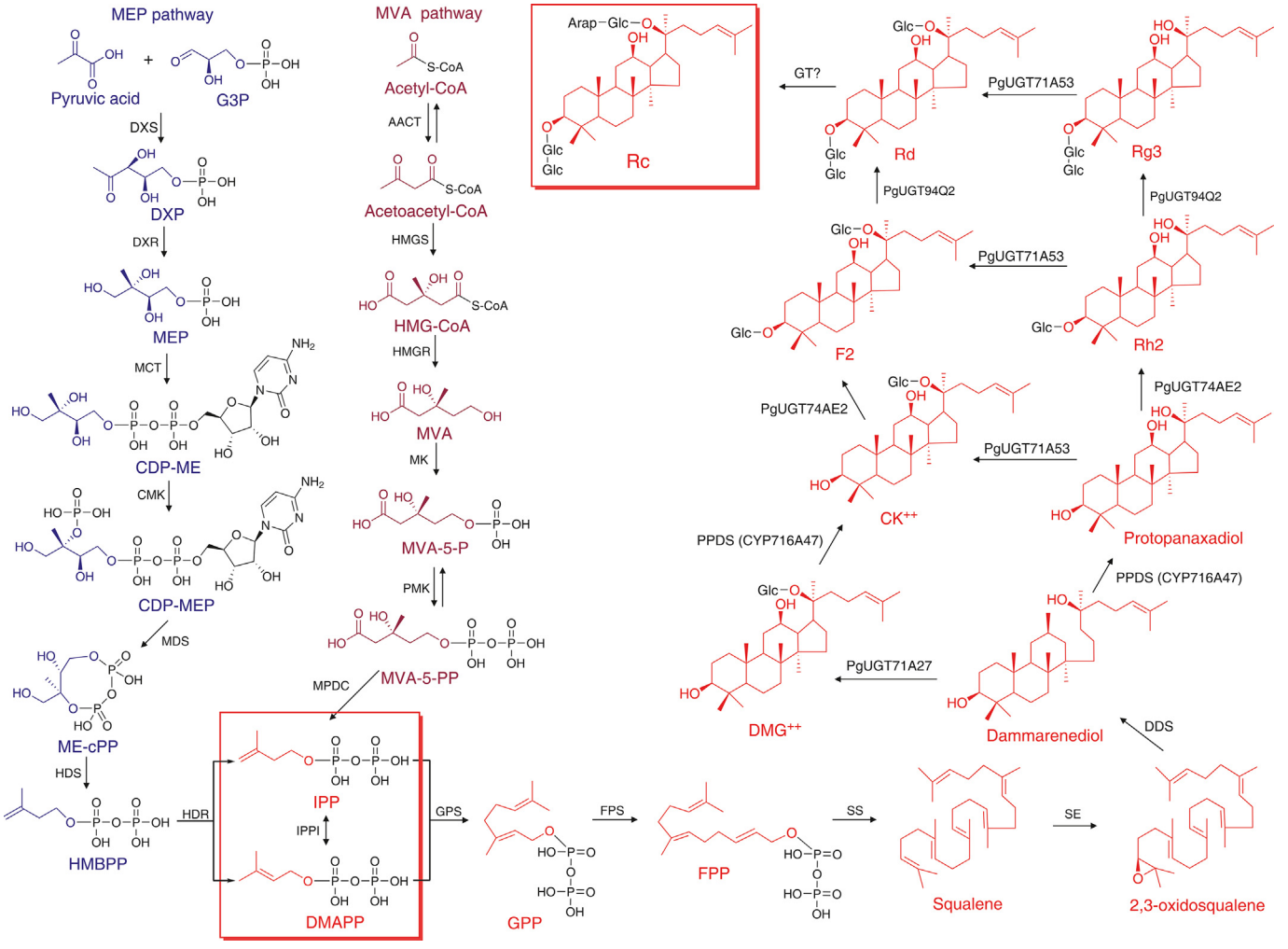

Fig. 1. The putative biosynthetic pathway of ginsenoside Rc. MEP: 2-C-methyl-D-erythritol-4-phosphate; DXP: 1-deoxy-D-xylulose 5-phosphate; DXS: DXP synthase; G3P: glyceraldehyde 3-phosphate; MCT: MEP cytidylyltransferase; CDP-ME: 4-(cytidine 5′-diphospho)-2-C-methyl-D-erythritol; CMK: 4-(cytidine 5′-diphospho)-2-C-methyl-D-erythritol kinase; MDS: 2-C-methyl-D-erythritol-2,4-cyclodiphosphate synthase; ME-cPP: 2-C-methyl-D-erythritol 2,4-cyclodiphosphate; HDS: 4-hydroxy-3-methylbut-2-enyl-diphosphate synthase; HMBPP: 4-hydroxy-3-methylbut-2-enyl diphosphate; MVA: mevalonate; AACT: acetyl-CoA C-acetyltransferase; HMGS: 3-hydroxy-3-methylglutaryl (HMG)-CoA synthase; HMGR: HMG-CoA reductase; MK: MVA kinase; MVA-5-P: MVA-5-phosphate; PMK: phospho-MVA kinase; MVA-5-PP: MVA-5-pyrophosphate; MPDC: diphospho-mevalonate decarboxylase; IPP: isopentenyl diphosphate; IPPI: IPP delta-isomerase; DMAPP: dimethylallyl diphosphate; GPS: geranyl diphosphate synthase; GPP: geranyl diphosphate; FPS: farnesyl diphosphate synthase; FPP: farnesyl pyrophosphate; SS: squalene synthase; SE: squalene epoxidase; DDS: damarenediol-II synthesis; DMG: 20S-O-β-(D-glucosyl)-dammarenediol II; PPDS: protopanaxadiol synthase; GT: glycosyltransferases.

electrophile DMAPP to form C10-geranyl pyrophosphate (GPP). GPP can then bind with another IPP to produce farnesyl pyrophosphate (FPP) under the action of farnesyl diphosphate synthase. Squalene synthase catalyzes the condensation of two molecules of FPP (C15) to form C30-squalene, a common precursor for the biosynthesis of triterpenes and phytosterols [30]. Squalene is further oxidized by squalene epoxidase to produce (3*S*)-2,3-oxidosqualene. Subsequently, oxidosqualene cyclases (OSCs) catalyze the cyclization of (3*S*)-2,3-oxidosqualene, which is the first step in the biosynthesis of various triterpenoid saponins and phytosterols [31]. Several functionally distinct OSCs have been identified to date [32,33]. Among them, damarenediol-II synthesis catalyzes the cyclization of (3*S*)-2,3-oxidosqualene to dammarenediol [34]. Once the basic triterpene skeleton is formed, it undergoes hydroxylation by cytochrome P450s and glycosylation by uridine diphosphate-dependent glycosyltransferases to yield various ginsenosides [24,35–37]. For instance, PgCYP716A47 could oxidize C-12 of dammarenediol to produce protopanaxadiol (PPD); PgUGT74AE2 and its two homologs PgUGT74AE4 (UGTPg45) and Pg3-O-UGT1 could catalyze the C3—OH glycosylation of PPD to generate ginsenoside Rh2; PgUGT94Q2 (UGTPg29) and its homologue Pq3-O-UGT2 could transfer glucose onto the C-2' hydroxyl group of the first glucose residue at C-3 of ginsenoside Rh2 to generate ginsenoside Rg3; and PgUGT71A53 (UGTPg1) could catalyze C-20 of ginsenoside Rg3 to synthesize ginsenoside Rd, which then further generates ginsenoside Rc. In addition, PgUGT74AE2, PgUGT94Q2 (UGTPg29), and PgUGT71A53 (UGTPg1) have been shown to involve in other transformations of intermediates [37,38]. For example, PgUGT74AE2 was shown to catalyze the transfer of a glucose moiety from uridine diphosphate-glucose to the C3 hydroxyl groups of compound K, yielding ginsenoside F2; PgUGT94Q2 (UGTPg29) was demonstrated to transfer a glucose moiety from UDP-glucose to ginsenoside F2 to produce ginsenoside Rd; and PgUGT71A53 (UGTPg1) was found to act in the glycosylation of several intermediates, including PPD, dammarenediol, and ginsenoside Rh2 at C-20 positions for the generation of compound K, 20*S*-O-β-(D-glucosyl)-dammarenediol II, and ginsenoside F2, respectively.

3. Extraction and quantification of ginsenoside Rc

Ginsenoside Rc represents the predominant component in ginsenoside extract. Traditional extraction methods for ginsenosides encompass decoction, immersion, reflux, and soxhlet extraction. While these traditional methods offer certain advantages, they also exhibit limitations such as lengthy extraction times, low efficiency, high solvent consumption, compromised thermal stability, and loss of volatile components. In light of ongoing research on traditional pharmaceutical preparations, novel extraction methods have emerged, including foam separation, ultrasound-assisted extraction [39], microwave-assisted extraction [40], supercritical fluid extraction [41], and high-pressure and ultra-high-pressure extraction [42]. Recent investigations focusing on ginsenoside Rc extraction have explored biomimetic extraction [43], pulsed electric field extraction [44], matrix solid-phase dispersion extraction [45], and mechanochemical-assisted low eutectic solvent extraction [46]. These innovative techniques typically outperform conventional approaches in terms of yield rates, specificity, reduction in organic solvent usage, and minimized environmental impact.

After extraction, ginsenosides are commonly separated using various techniques such as solid-liquid separation, liquid-liquid separation (including high-speed counter-current chromatography and centrifugal partition chromatography), immunoaffinity chromatography, macroporous adsorbent resin-silica column chromatography, and ultrasonic silica column chromatography. Preparative liquid chromatography is employed to purify ginsenoside Rc obtained from extraction and separation. The structure of ginsenoside Rc can be determined through chemical and spectroscopic methods, which serve as valuable tools for future research. In a study investigating the latest editions of the Chinese Pharmacopoeia (CP), Japanese/Korean Pharmacopoeia (J/KP), US Pharmacopoeia (USP), and European Pharmacopoeia (EP) for the isolation of ginsenosides, Li et al. [47] found that all of these methods exhibited high extraction rates for ginsenoside Rc. Liquid chromatography yielded the following concentrations for ginsenoside Rc: CP (0.23 ± 0.013 mg/g), USP (0.20 ± 0.011 mg/g), EP (0.20 ± 0.012 mg/g), and J/KP (0.11 ± 0.006 mg/g). The extraction rate of ginsenoside contents can be influenced by factors such as ethanol concentration, liquid-solid ratio, extraction duration, and heating conditions.

Currently, various methods such as high-performance liquid chromatography, ultra-performance liquid chromatography, high-performance thin layer chromatography, liquid chromatography-tandem mass spectrometry, ultra-fast liquid chromatography, and other methods are employed for quantifying ginsenoside Rc in samples [48]. Researchers have consistently enhanced the initial detection methods and developed several straightforward, sensitive, and quick detection techniques to more accurately estimate the concentration of ginsenoside Rc in body fluids and explore its pharmacokinetic properties. For instance, Sun et al. [49] investigated the pharmacokinetics of ginsenoside Rc using the rapid resolution liquid chromatography coupled with quadruple-time-of-flight mass spectrometry technique, successfully detecting ginsenoside Rc metabolites in rat urine. Multiple sensitive methods, including ultra-high-performance liquid chromatography-tandem mass spectrometry [50] and ultra-performance liquid chromatography/quadrupole time-of-flight mass spectrometry (UPLC/Q-TOF-MS) [51] have also been developed for the quantification of ginsenoside Rc and other components.

4. Pharmacokinetic characteristics of ginsenoside Rc

A crucial step in the research and development of new drugs is comprehending the pharmacokinetic properties of natural chemical products or active chemicals. The pharmacokinetic properties of ginsenoside Rc have been investigated in increasing numbers of physiological and pathological models (Table 1) [48,50,52–56].

4.1. Physiological model

Currently, there are two main ways of administration of ginsenosides: intravenous administration and oral administration. Chu et al. [52] conducted a pharmacokinetic study on rats treated with 2 mg/kg ginsenoside Rc intravenously, and the parameters were as follows: half-life ($t_{1/2}$) (22.000 ± 1.900 h), area under the curve (AUC_{0-t}) (779.808 ± 18.558 mg·h/L), and $AUC_{0-\infty}$ (862.997 ± 19.811 mg h/L). The parameters of the rats after oral ginsenoside Rc were $t_{1/2}$ (23.600 ± 0.600 h), AUC_{0-t} (13.364 ± 3.876 mg h/L), and $AUC_{0-\infty}$ (14.990 ± 4.289 mg h/L), which indicated that ginsenoside Rc was quickly absorbed into the circulatory system and slowly eliminated in the body. Related pharmacokinetic parameters and results have also been reported in several other model studies [53–56]. Zhang et al. [54] investigated the pharmacokinetic changes of ginsenoside Rc in Beagle dogs after intravenous injection of Shenfu injection (2, 4, and 8 mL/kg) and found that the $t_{1/2}$ of ginsenoside Rc was relatively long (about 90 h). It was also found that the absolute oral bioavailability of ginsenoside Rc was about 0.17% [52], similar to that of other ginsenosides [57]. Although the ginsenoside Rc prototype drug is not well absorbed orally, it has been found that it

Table 1
Pharmacokinetics of ginsenoside Rc.

Experimental model	Experimental design	Sample	Detection method	Pharmacokinetic parameters										Refs.
				$t_{1/2}$ (h)	AUC_{0-t} (mg·h/L)	$AUC_{0-\infty}$ (mg·h/L)	MRT_{0-t} (h)	$MRT_{0-\infty}$ (h)	c_{max} (mg/L)	t_{max} (h)	V_d (L/h/kg)	CL (L/h/kg)	Bioavailability (%)	
Physiological model	Wistar rats (♂); ginsenoside Rc, 80 mg/kg, p.o.	Plasma	UHPLC-MS/MS	9.659 ± 1.093	/	229.541 ± 110.102	14.000 ± 0.390	/	7.741 ± 0.037	1.000 ± 0.010	/	647.808 ± 36.107	/	[50]
	Wistar rats (♂); ginsenoside Rc, 20 mg/kg, p.o.	Plasma	HPLC-MS/MS	23.600 ± 0.600	13.364 ± 3.876	14.990 ± 4.289	/	/	0.701 ± 0.292	1.100 ± 0.550	/		17.000	[52]
	Wistar rats (♂); ginsenoside Rc, 2 mg/kg, i.v.	Plasma	HPLC-MS/MS	22.000 ± 1.900	779.808 ± 18.558	862.997 ± 19.811	/	/	/	/	/	/	/	[52]
	SD rats (♂); saponins from the leaves of *Panax notoginseng* (containing ginsenoside Rc), 300 mg/kg, p.o.	Plasma	HPLC-MS/MS	23.900 ± 6.820	2.902 ± 0.220	3.311 ± 0.164	23.400 ± 2.400	33.940 ± 8.730	0.102 ± 0.005	4.330 ± 2.920	259.980 ± 70.710	/	/	[53]
	Beagle dogs (♀+♂); Shenfu injection (containing 68.9 μg/mL ginsenoside Rc), 2 mL/kg, i.v.	Plasma	HPLC-MS/MS	81.910 ± 19.150	96.800 ± 23.770	154.050 ± 52.230	118.700 ± 27.640	/	2.490 ± 0.490	1.000	1.100 ± 0.200	0.010 ± 0.000	/	[54]
	Beagle dogs (♀+♂); Shenfu injection (containing 68.9 μg/mL ginsenoside Rc), 4 mL/kg, i.v.	Plasma	HPLC-MS/MS	92.000 ± 9.220	154.050 ± 52.230	259.480 ± 83.030	133.250 ± 13.310	/	4.380 ± 1.260	1.000	1.500 ± 0.340	0.010 ± 0.000	/	[54]
	Beagle dogs (♀+♂); Shenfu injection (containing 68.9 μg/mL ginsenoside Rc), 8 mL/kg, i.v.	Plasma	HPLC-MS/MS	93.010 ± 24.040	282.270 ± 18.110	473.090 ± 81.660	134.720 ± 34.680	/	6.870 ± 2.020	1.000	1.550 ± 0.180	0.010 ± 0.000	/	[54]
	SD rats (♂); *Panax notoginseng* saponins (containing 627.8 μg/mL ginsenoside Rc), 400 mg/kg, i.g.	Plasma	UPLC-MS/MS	36.440 ± 26.650	0.167 ± 0.051	196.540 ± 47.120	/	/	0.005 ± 0.002	6.250 ± 5.360	/	/	/	[55]
	SD rats (♂); ginsenosides (containing 12.3% ginsenoside Rc), 200 mg/kg, i.g.	Plasma	HPLC-MS/MS	31.500 ± 3.800	22.600 ± 8.300	25.900 ± 9.600	32.500 ± 1.600	/	0.585 ± 0.223	11.200 ± 1.790	/	8.580 ± 2.600	/	[56]
Pathological model	Chronic heart failure Wistar rats (♂); YiQiFuMai injection (containing ginsenoside Rc), 543 mg/kg, i.v.	Plasma	UFLC-MS/MS	29.810 ± 5.030	/	30.485 ± 10.459	/	/	/	/	/	0.002 ± 0.001	/	[48]
	Depressive male Wistar rats; ginsenoside Rc, 80 mg/kg, p.o.	Plasma	UHPLC-MS/MS	8.170 ± 0.880	/	295.337 ± 165.908	16.589 ± 1.745		12.497 ± 0.809	1.000 ± 0.010	/	450.788 ± 23.974	/	[50]

/: no data. $t_{1/2}$: elimination half-life; AUC_{0-t}: area under the concentration-time curve from 0 to t; $AUC_{0-\infty}$: area under the concentration-time curve from 0 h to time infinite; MRT: mean residence time; c_{max}: the maximum value of concentration; t_{max}: peak time; V_d: volume of distribution; CL: clearance; SD: Sprague-Dawley; p.o.: per os; i.v.: intravenously; i.g.: intragastrically; UHPLC-MS/MS: ultra-high performance liquid chromatography-tandem mass spectrometry; HPLC: high performance liquid chromatography; UPLC: ultra-performance liquid chromatographyy; UFLC: ultra-fast liquid chromatography.

could be metabolized into other products by gut microbiota to play a pharmacological role [58,59]. In vitro studies on the metabolism of ginsenoside Rc by human gut microbiota showed that ginsenoside Rc could be metabolized into compound K and PPD by the human fecal microbial community in anaerobic incubation environments [58], which was consistent with the results of intestinal microbial metabolites after oral ginsenoside Rc in rats [49]. In addition, it was confirmed that Bifidobacterium adolescentis could convert ginsenoside Rc to Rd [59]. These studies suggest that human and animal intestinal anaerobe (such as *bifidobacterium* and *Lactobacillus delleri*) have the ability to biotransform ginsenoside Rc, leading to its metabolism into other products by gut microbiota before absorption, thus affecting its bioavailability [59,60].

After entering the blood circulation, drugs first quickly enter the lungs, kidneys, heart, brain, liver, and other organs with large blood perfusion volume, distribute to other tissues, and finally achieve dynamic balance. Sun et al. [49] observed two-compartment pharmacokinetic characteristics of ginsenoside Rc in a rat model of intravenous injection of 0.4 mg/kg, and the $t_{1/2}$ of ginsenoside Rc was $t_{1/2\alpha} = 7.300 \pm 1.130$ min and $t_{1/2\beta} = 1091.670 \pm 173.180$ min, respectively, and AUC = 1701.190 ± 144.810 μg·min/mL. These results indicated that ginsenoside Rc was widely distributed in vivo with high plasma protein binding rate and a relatively large distribution coefficient. Kang et al. [56] detected six kinds of ginsenosides in plasma after the rats were given 200 mg/kg total ginsenosides intragaically. The exposure degree and half-rate period of ginsenosides of diol type, including ginsenoside Rc, were significantly higher than those of triol-type ginsenoside. The results of the tissue distribution study in this research also indicated that ginsenoside Rc was primarily distributed in the gastrointestinal tract, with small amounts found in organs such as the heart, liver, and kidneys, while trace amounts were detected in the brain [56]. These results indicated that ginsenoside Rc could be distributed to various tissues along the blood circulation and even penetrate the blood-brain barrier to some extent.

It is suggested that there are differences in the metabolites of ginsenoside Rc after intravenous administration and oral administration. Studies on intravenous administration of ginsenoside Rc in rats showed that part of it was excreted by urine and partially metabolized into Mb and Mc, and most of the ginsenoside Rc was converted to Mc and compound K in the gastrointestinal tract after oral administration [49]. The difference in metabolites of the two drug delivery routes may be due to the transformation of ginsenoside Rc through the digestive tract through contact with colonized gut microbiota after oral administration [59,60]. Jeon et al. [61] found another phenomenon that needs attention. After oral administration of red ginseng extract in rats and mice, there were significant species differences in the pharmacokinetics of plasma ginsenosides. Although ginsenoside Rc is characterized by high plasma exposure, short absorption time (t_{max}), and $t_{1/2}$ in both animal models, it is suggested that animal models should be carefully selected according to the classification of concern when carrying out ginsenosides related pharmacological studies.

4.2. Pathological model

Drugs are used to treat diseases, and patients are the ultimate consumers of medicines. Therefore, it is also essential to study the pharmacokinetics of drugs in disease states, which have higher clinical relevance and reference value. The pharmacokinetics of ginsenoside Rc in different disease models have been studied. In a 14-day study of 10 subjects with stable angina pectoris, the pharmacokinetics of ginsenoside Rc in Shengmai injection continued to conform to the two-compartment pharmacokinetic characteristics in patients with angina pectoris [62]. Zheng et al. [48] measured the contents of 10 kinds of ginsenosides in the plasma of rats with chronic heart failure (CHF) after intravenous administration of YiQiFuMai injection. The results showed that the ginsenosides in the plasma of CHF rats were gradually eliminated at different rates, and the elimination of ginsenoside Rc was the slowest. $AUC_{0-\infty}$ was 30.485 ± 10 459 mg·h/L, $t_{1/2}$ was 29.810 ± 5.030 h, and clearance rate (CL) was 0.002 ± 0.001 L/h/kg. Du and Jiang [50] found that compared with the normal rats, the peak concentration (c_{max}) and the bioavailability of ginsenoside Rc in depressed rats were significantly higher. Therefore, it was speculated that the pathological state might affect the pharmacokinetic characteristics of ginsenoside Rc in rats.

5. Anti-MetS effect of ginsenoside Rc

With the continuous improvement of extraction and quantification methods of ginsenoside Rc and the ongoing development of pharmacokinetic research, the pharmacological effects of ginsenoside Rc have drawn growing interest. Numerous in vivo and in vitro studies have revealed that ginsenoside Rc has therapeutic effects on obesity, diabetes, atherosclerosis, NAFLD, and OA and is a potential intervention agent for MetS (Table 2) [51,63–74]. What is worth mentioning is that the anti-MetS effect of ginsenoside Rc is characterized by multiple organs, multiple targets, and multiple ways (Fig. 2).

5.1. Obesity

In recent decades, the prevalence of obesity has been dramatically increasing in both developing and developed countries, posing significant challenges to economic and social development [75]. The use of complementary and alternative therapies from the Eastern countries in treating obesity is drawning extensive attention due to overall adverse effects and weight rebound after discontinuation of weight loss tablets [76]. Multiple studies have demonstrated that ginsenoside Rc exerts an anti-obesity effect (Table 2) [63–68].

Obesity is characterized by an increase in adipose tissue mass caused by an increase in the number and size of adipocytes [77]. A study found that mice fed a high-fat diet (HFD) lost 12.3% of their body weight after the treatment with ginsenoside Rc and exhibited a decrease in fat mass while maintaining lean mass [63]. Ginsenoside Rc treatment can reduce adipogenesis in rat epididymal adipocytes [67]. All the above studies suggest that ginsenoside Rc has an anti-obesity effect. A series of studies have explored the mechanisms of the weight loss effect of ginsenoside Rc. The fat-forming transcription factor CCAAT/enhancer binding protein α (C/EBPα) and peroxisome proliferator-activated receptor-γ (PPARγ) regulate the differentiation of preadipocytes into mature adipocytes, thereby affecting the number of adipocytes [78]. Ginsenoside Rc was discovered to limit the differentiation of adipocytes 3T3-L1 and reduce triglyceride content in adipocytes by down-regulating C/EBPα and PPARγ concentration dependently [68]. Ginsenoside Rc treatment can significantly reduce the weight of obese mice induced by an HFD and alleviate lipid metabolism disorders. Its mechanism is related to the activation of the sirtuin 6/AMP-activated protein kinase (SIRT6/AMPK) pathway and the up-regulation of PPARγ coactivator l alpha (PGC-1α) and PPARα in skeletal muscle, thereby promoting the oxidative decomposition of fatty acids [64]. In addition, the excessive intake of dietary fat is also a major contributing factor to obesity. Pancrelipases is responsible for the hydrolysis of dietary fats in the small intestine and is necessary to absorb fat in the intestine [79]. It has been found that the total saponins of stem and leaves and various monomers of American ginseng can reduce the weight of periuterine fat in female mice

Table 2
In vitro and in vivo studies on the anti-metabolic syndrome (MetS) effect of ginsenoside Rc.

Diseases	Research models	Treatments	Pharmacological effects	Mechanisms	Refs.
Obesity	Mice fed an HFD	In vivo: 5, 10, or 20 mg/kg/day ginsenoside Rc, 4 weeks, i.p.	Reduced body weight and fat mass	/	[63]
	Mice fed an HFD	In vivo: 20 mg/kg/day ginsenoside Rc, 4 weeks, i.p.	Reduced body weight and alleviate lipid metabolism disorders	Increased oxidative decomposition of fatty acids	[64]
	Mice fed an HFD	In vivo: diet with 1% or 3% crude saponins (containing ginsenoside Rc), 8 weeks In vitro: 0.5 g/L ginsenoside Rc for pancrelipases activity experiment	Reduced parametrial adipose tissue weight	Inhibited pancrelipase activity	[65]
	Mice fed an HFD	In vivo: diet with 1% or 3% American ginseng saponins or ginsenosides (containing ginsenoside Rc), 8 weeks In vitro: 0.5 g/L ginsenoside Rc for pancrelipases activity experiment	Reduced parametrial adipose tissue weight	Inhibited pancrelipase activity	[66]
	C2C12 skeletal muscle cells	In vitro: 50 μM ginsenoside Rc	Enhanced fatty acid decomposition oxidation and mitochondrial oxidative phosphorylation	Activated SIRT6/AMPK pathway Increased expression of PGC-1α and PPARα	[64]
	Rat epididymal fat cells	In vitro: 100 and 300 mM ginsenoside Rc	Reduced lipogenesis	/	[67]
	3T3-L1 preadipocytes	In vitro: 25, 50, or 100 μM ginsenoside Rc, 12 days	Inhibited adipocyte differentiation	Decreased expression of C/EBPα and PPARγ	[68]
Diabetes and its complications	Mice fed an HFD	In vivo: 5, 10, or 20 mg/kg/day ginsenoside Rc, 4 weeks, i.p.	Reduced fasting blood glucose and blood insulin levels as well as alleviated glucose intolerance and insulin resistance	Reduced expression of *PGC-1α*, *PEPCK*, and *G6Pase* in the liver	[63]
	Mice fed an HFD	In vivo: 20 mg/kg/day ginsenoside Rc, 4 weeks, i.p.	Reduced blood glucose	Increased expression of SIRT6 in skeletal muscle	[64]
	Diabetic mice	In vivo: 20 mg/kg/day ginsenoside Rc, 4 weeks, i.g.	Alleviated aortic endothelial dysfunction	Activated the ACE2/Ang-(1−7)/Mas axis	[69]
	HUVECs cultured in high glucose medium	In vitro: 50 μM ginsenoside Rc, 24 h	Decreased ROS and proinflammatory cytokines	Activated the ACE2/Ang-(1−7)/Mas axis	[69]
	C2C12 skeletal muscle cells	In vitro: 50, 100, or 200 μM ginsenoside Rc, 1 h	Enhanced glucose uptake	Activated AMPK and MAPK	[70]
Atherosclerosis	*ApoE*$^{-/-}$ mice fed an HFD	In vivo: 40 mg/kg/day ginsenoside Rc, 12 weeks, i.g.	Reduced blood total cholesterol and LDL-C as well as decreased atherosclerotic lesion size and collagen content in aortic sinus	Changed the composition of gut microbiota and fecal metabolites	[71]
	Human umbilical vein endothelial cell line EAhy926 treated with TNF-α	In vitro: Shenfu injection (containing ginsenoside Rc) 0.1 μg/mL, 24 h	Enhanced cell viability and alleviated inflammatory response	Reduced expression and phosphorylation of NF-κB by ginsenoside Rc and other ingredients (based on network pharmacology analysis)	[51]
	Rat arterial smooth muscle cells	In vitro: 100 μg/mL ginsenoside Rc	Inhibited smooth muscle cell migration	/	[72]
NAFLD	Mice fed an HFD	In vivo: 5, 10, or 20 mg/kg/day ginsenoside Rc, 4 weeks, i.p.	Reduced liver and serum TG levels, AST/ALT levels Alleviated liver lipid accumulation, mitochondrial stress and intracellular redox dyshomeostasis	Activated the SIRT6-PPARα axis of liver	[63]
	Mouse primary hepatocytes	In vitro: 20, 40 μM ginsenoside Rc, 48 h	Reduced lipid accumulation	Increased liver SIRT6 Decreased H3K9ac and H3K56ac	[63]
	Mouse primary hepatocytes	In vitro: 50 μM ginsenoside Rc, 24 h	Reduced lipid accumulation	Increased liver SIRT6 and PPARα expression	[73]
Osteoarthritis	Human chondrocyte lines SW1353 treated with IL-1β	In vitro: 30 μM ginsenoside Rc, 24 h	Inhibition of cartilage matrix degradation	Decreased MMP-13 expression	[74]

/: no data. HFD: high-fat diet; i.p.: intraperitoneal injection; SIRT6: sirtuin 6; AMPK: AMP-activated protein kinase; C/EBPα: CCAAT/enhancer binding protein α; PPARγ: peroxisome proliferator-activated receptor-γ; PGC-1α: PPARγ coactivator 1 α; PEPCK: phosphoenolpyruvate carboxykinase; G6Pase: glucose-6-phosphatase; i.g.: intragastrically; ACE2: angiotensin converting enzyme 2; HUVECs: human umbilical vein endothelial cells; ROS: reactive oxygen species; MAPK: p38 mitogen-activated protein kinase; *ApoE*$^{-/-}$: apolipoprotein E-deficient; LDL-C: low-density lipoprotein cholesterol; TNF-α: tumor necrosis factor alpha; NF-κB: nuclear factor kappa B; NAFLD: non-alcoholic fatty liver disease; TG: triglyceride; AST: aspartate transaminase; ALT: alanine transaminase; H3K9ac: histone 3 lysine 9 acetylation; IL-1β: interleukin-1β; MMP-13: matrix metalloproteinase-13.

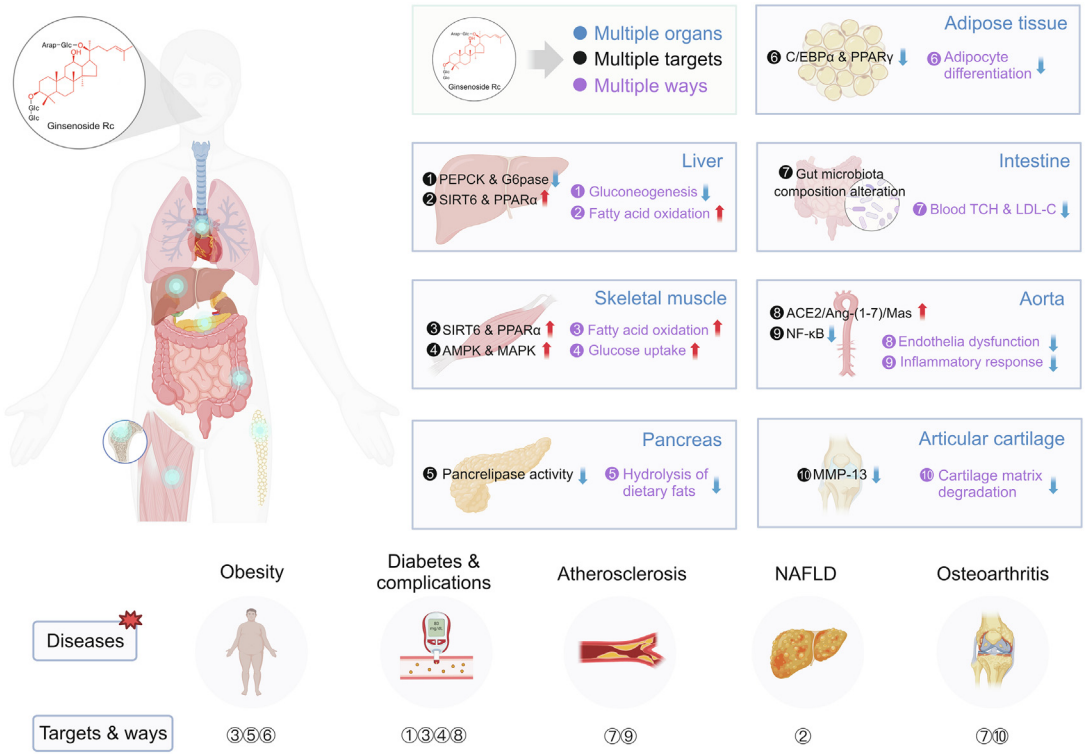

Fig. 2. The anti-metabolic syndrome effect of ginsenoside Rc is characterized by multiple organs, multiple targets, and multiple ways. PEPCK: phosphoenolpyruvate carboxykinase; G6Pase: glucose-6-phosphatase; SIRT6: sirtuin 6; PPARγ: peroxisome proliferator-activated receptor-γ; AMPK: AMP-activated protein kinase; MAPK: p38 mitogen-activated protein kinase; C/EBPα: CCAAT/enhancer binding protein α; TCH: total cholesterol; LDL-C: low-density lipoprotein cholesterol; ACE2: angiotensin converting enzyme 2; NF-κB: nuclear factor kappa B; MMP-13: matrix metalloproteinase-13; NAFLD: non-alcoholic fatty liver disease.

[65,66], and compared with other monomer saponins, ginsenoside Rc has the most potent inhibitory effect on pancrelipases activity [66,80]. Further in vitro studies have shown that the anti-obesity effect of ginsenoside Rc is realized through strong inhibition of pancrelipases rather than affecting the absorption of fatty acids by small intestinal brush membranous sacs [80]. In addition, a study on clinically obese women suggested that the anti-obesity mechanism of ginseng might be related to the changes in the composition of the host gut microbiota, including changes in the abundance of *Bifidobacterium* and *Eschella* [81]. Meanwhile, Xie et al. [71] found that ginsenoside Rc could improve the imbalance of intestinal flora (including *Bifidobacterium*) induced by HFD in mice, which further supported the potential anti-obesity effect of ginsenoside Rc. In conclusion, ginsenoside Rc may have anti-obesity effects by inhibiting the activity of pancrelipases, blocking the differentiation of adipocytes, promoting the oxidative decomposition of fatty acids, and regulating the gut microbiota.

5.2. Diabetes

Diabetes refers to an increase in blood glucose levels induced by decreased insulin secretion of pancreatic β cells or desensitization of peripheral effector cells to insulin, which is respectively divided into type 1 diabetes and type 2 diabetes (T2DM) [82]. T2DM accounts for about 90% of global diabetes cases [83] and is a complication closely related to MetS [84]. Clinical studies have found that ginseng can significantly reduce fasting blood glucose and glycated hemoglobin levels in T2DM patients [85,86]. Meanwhile, many studies have shown that ginsenoside Rc, as one of the active ingredients of ginseng, plays a vital role in its anti-diabetic effect (Table 2) [63,64,69,70].

A network pharmacological study on ginsenosides suggested that ginsenoside Rc could alleviate insulin resistance and treat diabetes by acting on multiple targets in collaboration with other ginsenosides [87]. Another study further found that ginsenoside Rc intake significantly reduced fasting glucose and insulin levels in mice fed an HFD, effectively alleviating their glucose intolerance and insulin resistance, which was associated with the downregulation of liver glycogenic genes *PGC-1α*, phosphoenolpyruvate carboxykinase (*PEPCK*), and glucose-6-phosphatase (*G6Pase*) [63]. In addition, ginsenoside Rc may also play a hypoglycemic role by regulating the metabolism in skeletal muscle. It is known that skeletal muscle is responsible for consuming over 80% of postprandial glucose load [88], and reduced glucose uptake by skeletal muscle can lead to elevated blood glucose levels [89]. The AMPK signaling pathway mediates the non-insulin-dependent glucose uptake pathway in muscle [90], and p38 mitogen-activated protein kinase (MAPK) is a component of the AMPK signaling pathway [91]. Moreover, reactive oxygen species (ROS) produced in muscle can activate AMPK related glucose uptake cascade reactions [92]. An in vitro study revealed that ginsenoside Rc could concentration-dependently trigger ROS generation in mouse myoblasts and increase the phosphorylation of AMPK and MAPK, promoting glucose uptake [70]. Notably, ginsenoside Rc showed no discernible impact on the phosphatidylinositol 3 kinase-mediated insulin-dependent glucose uptake pathway [88]. Moreover, SIRT6 extensively regulates glucose metabolism in skeletal muscle and is a potential therapeutic target for diabetes [93]. Recent studies have shown that the expression of SIRT6 increases in skeletal muscle after ginsenoside Rc administration, thereby reducing blood glucose levels in mice fed an HFD [64].

In addition, ginsenoside Rc can also alleviate the complications of diabetes. Cardiovascular disease is the main complication leading to the death of patients with T2DM [94]. Vascular endothelial dysfunction is the primary mediator of diabetic cardiovascular complications [95], and activation of angiotensin-converting enzyme 2 (ACE2) can ameliorate endothelial dysfunction [96]. An in vitro study found that ginsenoside Rc promoted ACE2 expression in human umbilical vein endothelial cells (HUVECs), thereby relieving endothelial dysfunction in HUVECs induced by high glucose medium, manifested by reduced ROS and pro-inflammatory cytokines. The in vivo study further demonstrated that ginsenoside Rc could alleviat aortic endothelial dysfunction in diabetic mice by activating the ACE2/Ang-(1–7)/Mas axis [69]. Diabetic nephropathy is also a common complication of diabetes. A network pharmacology study proposed that ginsenoside Rc in Shenqi Jiangtang granules could play an anti-diabetic nephropathy role through multiple targets and multiple pathways [97].

In brief, ginsenoside Rc can produce a hypoglycemic effect by inhibiting liver glucose production and regulating skeletal muscle glucose metabolism, and can also alleviate cardiovascular diseases and diabetic nephropathy and other complications caused by diabetes.

5.3. Atherosclerosis

Atherosclerosis is a chronic inflammatory vascular disease resulting from the cumulative effects of multiple risk factors on the arterial wall [98]. It is a major contributor to cardiovascular diseases, including myocardial infarction and ischemic cardiomyopathy, which are leading causes of global mortality [99]. Ginseng is widely recognized for its potential in treating cardiovascular disorders [100]. Several studies have demonstrated the anti-atherosclerotic effects of ginsenoside Rc, the active component of ginseng (Table 2) [51,71,72].

Hypercholesterolemia is a major risk factor for the formation and progression of atherosclerosis [101]. The formation of atherosclerotic plaque induced by high levels of low-density lipoprotein cholesterol (LDL-C) in the blood involves a series of crucial molecular events. LDL undergoes oxidative modification after accumulation in the arterial intima, transforming into oxidized LDL (ox-LDL) and causing infiltration of macrophages. Macrophages phagocytose ox-LDL and transform into foam cells, producing ROS and inducing inflammation. Ox-LDL, ROS, and proinflammatory cytokines cause endothelial dysfunction, exacerbating atherosclerosis development [102,103]. Moreover, vascular smooth muscle cells can invade early atherosclerotic lesions and expand plaque [104]. Ginsenoside Rc can affect several key molecular events in the above process and thus exert anti-atherosclerosis effects. A study found that ginsenoside Rc intake could significantly decrease the levels of total cholesterol, LDL-C, and triglycerides in the blood of apolipoprotein E-deficient mice fed an HFD, which reduces the size of atherosclerotic lesions and collagen content in the aortic sinus. It is worth noting that the lipid-lowering effect of ginsenoside Rc is related to changes in the composition of intestinal microbiota and fecal metabolites in mice [71]. Ginsenoside Rc can also slow the development of atherosclerosis by alleviating endothelial dysfunction. Nuclear factor kappa B (NF-κB) activates a series of inflammatory responses and plays a central role in the pro-inflammatory activation of the endothelium in atherogenesis [103,105]. It was found that Shenfu injection has an anti-inflammatory effect and can reduce the phosphorylation level of NF-κB in HUVECs. Meanwhile, ginsenoside Rc was screened as one of the effective components that could inhibit NF-κB in Shenfu injection by network pharmacological analysis and bioactivity-integrated UPLC/Q-TOF-MS [51]. Besides, ginsenoside Rc is also an essential inhibitor of NF-κB in YiQiFuMai injection [106,107]. Additionally, another study discovered that ginsenoside Rc could inhibit the migration of arterial smooth muscle cells induced by platelet-derived growth factor and smooth muscle cell-derived migration factor in a concentration dependent manner, which may prevent atherosclerotic lesions from intimal thickening [72]. In conclusion, ginsenoside Rc can treat atherosclerosis by lowering lipid, alleviating endothelial dysfunction, and preventing smooth muscle cell migration.

5.4. NAFLD

NAFLD is a chronic liver disease characterized by the infiltration of hepatocytes with steatosis, affecting approximately 25% of the global population. Given the potential progression of NAFLD to cirrhosis and hepatocellular carcinoma, it is essential to implement medication and other treatment measures to prevent disease advancement [108]. Currently, there remains a dearth of systematic clinical research on the efficacy of ginseng in treating NAFLD [109]. However, animal studies have confirmed the anti-NAFLD effect of ginsenoside Rc derived from ginseng (Table 2) [63,73].

It is known that the blockage of hepatic fatty acid oxidation can induce lipid accumulation in the liver and trigger NAFLD [110]. PPARα regulates fatty acid β oxidation and plays a vital role in maintaining lipid homeostasis in the liver [111], and SIRT6 can promote liver fatty acid oxidation by activating PPARα [112]. Studies on mice and primary liver cells have shown that ginsenoside Rc treatment can reduce serum and liver triglyceride levels in HFD-fed mice and alleviate hepatic steatosis, and the mechanism is related to the activation of liver SIRT6-PPARα axis, enhancement of fatty acid oxidation in liver cells, and alleviation of mitochondrial stress and intracellular redox dyshomeostasis by ginsenoside Rc [63]. Notably, liver *SIRT6*-specific knockout significantly attenuated the activation effect of ginsenoside Rc on hepatic fatty acid oxidation [63]. Another study also verified that ginsenoside Rc could promote the expression of SIRT6 and PPARα and enhance fatty acid oxidation in mouse primary hepatocytes [73]. In addition, ginsenoside Rc is also an effective activator of SIRT1 [113,114], and SIRT1 activation can promote fatty acid oxidation and reduce lipid accumulation in the liver [115], which suggests that ginsenoside Rc may promote hepatic fatty acid oxidation and alleviate NAFLD by up-regulating SIRT1. Generally, ginsenoside Rc can treat NAFLD by promoting hepatic fatty acid oxidation.

5.5. Osteoarthritis

OA is a chronic joint disease characterized by the destruction of articular cartilage and persistent pain, which is a major cause of disability in the elderly [116]. The traditional view holds that OA is a chronic degenerative disease. Currently, based on the close relationship between OA and MetS, some studies have proposed that OA also belongs to the category of MetS [117]. In a clinical trial, postmenopausal women with OA experienced less pain and had better Disabilities of the Arm, Shoulder and Hand (DASH) scores after taking ginseng [118]. Experimental studies have found that ginsenoside Rc is an essential component of ginseng for its anti-OA effect (Table 2) [74].

The mechanical support effect of articular cartilage depends on the integrity of its extracellular matrix, and the reduction of the cartilage matrix can induce OA [119]. Matrix metalloproteinase-13 (MMP-13) is involved in the degradation of the cartilage matrix and is the key enzyme causing cartilage degeneration [120]. An in vitro study found that ginsenoside Rc inhibited MMP-13

expression in human chondrocyte lines treated with interleukin-1β, suggesting that ginsenoside Rc raises the possibility of treating OA by inhibiting cartilage matrix degradation [74]. In addition, the main manifestations of MetS, such as hyperglycemia and hypercholesterolemia, can aggravate the occurrence and development of OA [121,122]. Two in vivo studies showed that ginsenoside Rc intake significantly reduced blood glucose and total cholesterol levels in mice fed an HFD [63,71], which reduced their risk of OA. In conclusion, ginsenoside Rc can retard the progression of OA by inhibiting the cartilage matrix degradation and lowering blood glucose and lipids.

6. Safety of ginsenoside Rc

Ginsenoside Rc, a biologically active compound found in commonly used medicinal and health care products, has garnered significant attention. Animal studies have revealed that administration of ginsenoside Rc at doses of 5 or 20 mg/kg/day ginsenoside Rc (for 5 days a week over a 5-week period) alleviated arthritis, gastritis, and hepatitis in mice, without affecting their toxicological parameters or causing gastrointestinal irritation [123]. Peritoneal injection of 5 or 10 mg/kg/day ginsenoside Rc for 10 consecutive days demonstrated a reduction in acetaminophen-induced hepatotoxicity, promoting liver repair and improving survival rates in mice [124]. In the most recent series of studies, ginsenoside Rc was found to mitigate myocardial damage in rats and mice [113,125–127] and provide neuroprotective effects in mice [114]. Red ginseng extract containing 13.0 ± 1.7 mg/day ginsenoside Rc was given to 15 healthy male subjects by Choi et al. [127] for a single or consecutive 15 days and found that the subjects had good tolerance, stable blood pressure and body temperature, and normal liver function, indicating that ginsenoside Rc at this dose is safe and tolerable. Overall, these investigations demonstrate the protective effects of ginsenoside Rc at effective doses without notable hepatotoxicity or other side effects in both healthy individuals and rodents.

In addition to adults, ginseng is commonly used by special groups such as pregnant women. This is often attributed to various perceived benefits including its potential to support pregnancy and fetal health, promote general well-being, and alleviate symptoms of the common cold [128]. A prospective study on the use of Chinese herbal medication during pregnancy revealed that up to 31.7% of expectant mothers used ginseng-containing Chinese herbal medicines and 24.8% took angelica (both of which include ginsenoside Rc) [128]. Chan et al. [129] observed the embryotoxic effects of different types of ginsenosides on rat embryos cultivated in vitro, and discovered that 50 μg/mL ginsenoside Re caused substantial developmental delays in rat embryos while 5.0 and 50 μg/mL ginsenoside Rc had no negative effects on rat embryo development. According to Hu et al. [130], ginsenoside Rc could stimulate the expression of glutathione peroxidase at concentrations of 45 and 90 μg/mL, which could help the development of the rat embryonic brain in vitro. To date, no definitive reports of ginsenoside Rc toxicity have been documented in relation to adult or embryonic development.

Currently, ginsenoside Rc-containing medications available in the market are often in the form of granules, pills, or injections derived from extracts of Chinese medicinal plants. However, variations in origin, extraction methods, formulations, authenticity, and other factors contribute to significant differences in the ginsenoside content among various products [131]. The lack of specific toxicity studies for individual types of ginsenosides can be attributed to the diverse array of ginsenosides found in pharmaceutical preparations. Consequently, future research should focus on investigating the specific toxic effects of different ginsenoside types to facilitate their accurate and safe clinical utilization.

7. Opportunities for ginsenoside Rc in studies and therapeutic applications related to metabolic syndrome

7.1. Investigating mechanisms in depth

With the development of metabolomics, transcriptomics, proteomics, and other technologies during the past several years, researchers have attached increasing importance to identify targets and mechanisms through multi-omics analysis in the study of natural pharmaceuticals [132]. On the basis of multi-omics analysis, a number of studies have recently examined the function and mechanism of arabinoxylan oligosaccharides [133], kaempferol [134], and ginsenoside Rb1 [135] in the treatment of metabolic diseases and have successfully discovered corresponding differential metabolites, important regulatory pathways, or biomarkers. Therefore, the use of multi-omics analysis methods, supplemented by fusion technologies in artificial intelligence, machine learning, and other fields, will be the promising program in the follow-up ginsenoside Rc anti-MetS studies [136], followed by the validation of the therapeutic effect of ginsenoside Rc on animal disease models, combined with in vitro studies and population experiments. This research strategy will offer more thorough and precise details regarding the molecular targets and impact pathways of ginsenoside Rc against MetS and other disorders and create a more solid foundation for its therapeutic application.

It is crucial to find shared therapeutic routes to prevent and treat different phenotypes of MetS since it frequently involves harm to diverse systems. Regarding that the anti-MetS effect of ginsenoside Rc is implicated in a number of disorders, such as anti-obesity, diabetes, and NAFLD, the activation of the SIRT1 and SIRT6/AMPK pathways may be one of the key mechanisms of ginsenoside Rc anti-MetS [63,64,70,73,115]. The paper's conclusion implies that the anti-MetS effect of ginsenoside Rc is characterized by multiple organs, multiple targets, and multiple ways in nature. Therefore, identifying the common mechanisms underlying the pharmacological effects of ginsenoside Rc will help advance its application in disease intervention and treatment.

7.2. Hightlihgting the regulatory effect on gut microbiota

As the second-largest genome in the human body, the gut microbiota plays a variety of physiological roles in the liver, gut, brain, and other organs. Due to their crucial function in host physiological and pathological events, the gut and the microbial populations have recently received a lot of attention [137]. According to the most recent research, gut flora problem poses a serious risk for developing MetS [138]. Obesity, hyperglycemia, insulin resistance, and dyslipidemia can result from abnormal strains of *Firmicutes*, *Bacteroides*, *Actinomyces*, and *Proteus* [138,139]. Therefore, the gut microbiota may be a potential target for traditional drugs to treat MetS. According to animal research, ginsenoside Rc can reverse the effects of HFD on the intestinal flora of mice including *Firmicutes*, *Bacteroides*, *Lactobacillus*, and *Bifidobacterium* [71]. The in vitro culture tests of intestinal bacteria in healthy individuals have further supported the impact of ginsenoside Rc on *Firmicutes*, *Proteobacteria*, and *Bacteroidetes* [140]. However, whether ginsenoside Rc exerts its anti-MetS effects by specifically regulating the aforementioned strains needs further investigation and confirmation.

Understanding the regulatory effect of ginsenoside Rc on gut microbiota can aid in a more thorough understanding of the anti-MetS and other pharmacological effects of ginsenoside Rc.

7.3. Focusing on drug interactions

The analysis of drug interaction studies is a crucial stage in the development of new drugs. Due to the many pharmacological effects of ginseng preparations, they are frequently utilized as healthcare items or adjuvants in conjunction with other prescription medications. For its sensible clinical application, it is crucial to ascertain whether it has antagonistic effects, synergistic effects, or harmful effects with common drugs. According to previous studies, taking ginseng preparations with digoxin, insulin, anticoagulants, monoamine oxidase inhibitors, stimulants, or hormone medications should be avoided [141]. However, research on ginsenoside Rc monomer's potential medication interactions is still in its infancy. Studies suggest that of all types of ginseng saponin, ginsenoside Rc is the novel and most selective inhibitor of uridine 5′-diphosphoglucuronosyltransferase 1A9 (UGT1A9) in human liver microsomes [142]. This study also reveals that given the low plasma concentration of ginsenoside Rc in healthy subjects (0.01 μM), it does not typically induce additional co-administered drug interactions associated with UGT1A9 metabolism. Jeon et al. [143] studied 12 kinds of ginsenosides co-administered with valsartan in rats and showed that, unlike most PPD-type ginsenosides, ginsenoside Rc does not affect the liver and gallbladder excretion of valsartan in vivo by inhibiting organic anion transporter polypeptide 1B3. This may be due to the high protein affinity, hydrophilicity, and large volume of ginsenoside Rc, making it difficult to distribute in large quantities in the liver. Recent research indicates that ginsenoside Rc is a generally safe ginsenoside type and does not readily lead to medication interactions. However, follow-up studies still need to maintain high attention to this problem to promote the successful clinical transformation of ginsenoside Rc application.

8. Conclusion

This paper provides an overview of recent studies to demonstrate the beneficial effects of ginsenoside Rc, an active substance derived from traditional herbs, on metabolic diseases such as obesity, diabetes, atherosclerosis, and NAFLD. These therapeutic actions of ginsenoside Rc are mediated through various signaling molecules, including C/EBPα, SIRT6, PPARα/γ, PGC-1α, PEPCK, G6Pase, ACE2, AMPK, NF-κB, and MMP-13. With further investigation into its mechanism of action, ginsenoside Rc holds promise as a potential medication for the prevention and treatment of MetS. Moreover, exploring the properties of ginsenoside Rc may inspire researchers to explore the potential of other natural saponins and plant-derived active substances as novel approaches to combat MetS.

Ginsenoside Rc is a well-tolerated compound with a favorable safety profile. It demonstrates rapid oral absorption, slow in vivo elimination, and a relatively long half-life (90 h), indicating its stable presence in the body, delayed onset, and potential for enhanced efficacy. Animal studies have shown its ability to regulate metabolic homeostasis, supporting the hypothesis that ginsenoside Rc could serve as a safe and effective intervention for MetS. However, several considerations must be addressed before ginsenoside Rc can be definitively introduced as a standalone therapeutic in clinical settings. The precise mechanism of action remains unclear, hindering further research, despite numerous reported preclinical benefits in MetS. Clinical data on monotherapy trials are lacking, and the effectiveness of ginsenoside Rc in combination with other medications remains unexplored. Additionally, comprehensive investigations into the pharmacokinetic properties of various administration routes in diverse disease models are required, as the pharmacokinetics of ginsenoside Rc vary across models and routes of administration. Simultaneously, research focusing on intestinal flora metabolism, nano-carrier design, and optimization of the functional group structure of ginsenoside Rc should be conducted to enhance its bioavailability and deliver more targeted therapeutic effects.

In conclusion, numerous preclinical studies suggest the potential use of ginsenoside Rc in clinical trials for the treatment of MetS. However, the lack of clinical trials investigating the specific therapeutic effect of ginsenoside Rc in human MetS poses challenges in confirming its efficacy. To bridge the gap between preclinical research and clinical translation, well-designed double-blind, multicenter clinical trials are essential to evaluate the safety and efficacy of ginsenoside Rc in patients with MetS.

CRediT author statement

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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