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Review Article

Ginsenoside Rb2: A review of pharmacokinetics and pharmacological effects

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ABSTRACT

Ginsenoside Rb2 is an active protopanaxadiol-type saponin, widely existing in the stem and leave of ginseng. Rb2 has recently been the focus of studies for pharmaceutical properties. This paper provides an overview of the preclinical and clinical pharmacokinetics for Rb2, which exhibit poor absorption, rapid tissue distribution and slow excretion through urine. Pharmacological studies indicate a beneficial role of Rb2 in the prevention and treatment of diabetes, obesity, tumor, photoaging, virus infection and cardiovascular problems. The underlying mechanism is involved in an inhibition of oxidative stress, ROS generation, inflammation and apoptosis via regulation of various cellular signaling pathways and molecules, including AKT/SHP, MAPK, EGFR/SOX2, TGF-β1/Smad, SIRT1, GPR120/AMPK/HO-1 and NF-κB. This work would provide a new insight into the understanding and application of Rb2. However, its therapeutic effects have not been clinically evaluated. Further studies should be aimed at the clinical treatment of Rb2.

1. Introduction

Ginseng is a perennial plant belonging to the Araliaceae family, and it has been recorded and used as a medicine herb for thousands of years in East Asia [1]. To date, 13 species of ginseng have been identified, in which Panax ginseng Meyer (Asian ginseng) and Panax quinquefolius L (American ginseng) are the most well-known as function food [2,3]. Ginsenosides are a group of triterpene saponins and exhibit comprehensive bioactivities [4]. Nearly 150 ginsenosides have been isolated from the root, stem, fruits, leaves and flowers of ginseng [5]. Based on the chemical structure, ginsenosides are mainly divided into protopanaxadiol (PPD), protopanaxatriol (PPT), oleanolic acid type and ocotillol type [4].

Ginsenoside Rb2 is an active PPD-type saponin and widely distributed in different kinds and parts of ginseng. It is relatively rich in P. ginseng (0.073–0.421%) and Panax quinquefolius (0.194–0.219%), but in Panax japonicus and Panax noteginseng did not nearly exist [4]. In the ginseng, Rb2 is primarily concentrated in the stems, leaves and berries [5]. The molecular formula and structure of Rb2 is shown in Fig. 1, whose major differences from other PPDs are the sugar moiety in side chains [6]. Recently, pharmacokinetic properties of Rb2 in animal models have been extensively studied, but only a few relevant investigations in humans are reported. And many pharmacological studies have showed the comprehensive effects of Rb2 against diabetes, obesity, tumor, photoaging, virus infection and cardiovascular problems. To our knowledge, there is no published review to assess the pharmacological effects of Rb2 based on summarizing the current reliable evidence. Herein, this paper systematically summaries pharmacokinetic properties and pharmacological activities of Rb2,

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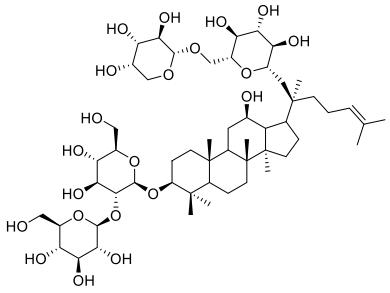

Fig. 1. Chemical structure of Rb2: 3-O-[b-D-Glucopyranosyl-(1–2)-b-D- glucopyranosyl]- 20-O-[a-L-arabinopyranosyl-(1–6)-b-D-glucopyranosyl]-20(S)-protopanaxadiol.

and it would provide a theoretical basis for further pharmaceutical studies and clinical application.

2. Pharmacokinetics

Pharmacokinetics determines the drug concentrations at the target site, and is crucial to play pharmacological effects. However, there is little report about the relevant reviews of Rb2. Thus, we summarized most studies that investigated its pharmacokinetics (Tables 1 and 2).

2.1. Preclinical pharmacokinetics

Absorption, distribution, metabolism and excretion (ADME) are key factors that influence tissue drug concentrations over time [7]. Zhao et al. [8] compared the similarities and differences between pharmacokinetic behaviors of Rb2 via oral and intravenous administration in rats (50 and 10 mg/kg, respectively). The area under the plasma concentration-time curve (AUC) of Rb2 with two administration methods were 9.7 ± 3.2 and 20006.3 ± 283.0 mg h/L respectively; maximum plasma concentrations (C_{max}) were 0.4 ± 0.1 and 198.1 ± 27 0.9 mg/L respectively; the bioavailability of Rb2 was only 0.08%. These data indicated the oral absorption of Rb2 was extremely low.

Poor oral absorption was mainly attributed to low permeability of Rb2 in the intestine, due to its large molecular mass, high hydrogen-bonding capacity and high molecular flexibility [9]. It was verified by the Caco-2 cell assay in vitro, in which the membrane permeability of Rb2 was poor with the Papp of 2.8×10^{-7} cm/s [10]. Another factor was that Rb2 was susceptible to degrade or bio-transform under gastric acid or intestinal bacteria [11]. Rb2 could be transformed to minor ginsenosides, including Rd, F2, compound O, compound Y and compound K, by the intestinal microflora, which were hardly present in unprocessed ginseng [12]. These minor ginsenosides were readily permeated into the bloodstream, and may have a competitive absorption against Rb2 [13]. In addition, Rb2 was a low water-soluble ginsenoside, resulting in irregular and incomplete absorption in the body. These factors may limit the absorption and exposure of Rb2 in plasma.

In another study, a single dose of 10.4 mg/kg ShenMai injection, a traditional Chinese herbal medicine composed of ginseng extract and Ophiopogonis radix, was injected to rats via tail vein [14]. The result showed Rb2 had a long half-life ($t_{1/2}$) with 75.4 ± 47.3 h, and it could be still detected in serum at 96 h after administration, indicating that its elimination was slow in serum. The long elimination process may be partly attributed to high plasma protein binding [15]. The tissue distribution affected the efficacy and duration of action. Rb2 could spread into the heart, liver, spleen, lung and kidney at 5 min after dosing, and the highest concentrations were in the lung and kidney. In addition, Rb2 could penetrate through the blood-brain barrier and rapidly transport into the brain. It was worth noting that Rb2 had a long-term accumulation risk in the kidney and brain. The excretion profile was determined by detecting the concentration of Rb2 in urine and feces. The results indicated that Rb2 was only excreted into urine and was not found in feces. The accumulating concentration of Rb2 in urine was low with 21.3 ± 8.5 ng from 0 to 96 h, and it was still detected in urine until 96 h after administration. It was showed that Rb2 excretion was slow and relatively uniform, which was consistent with its slow elimination in plasma and tissue [14].

2.2. Herb-drug interaction

The reported cases of herb-drug interactions are rapidly increasing, and influence the concentration of drugs within the plasma or tissue [15]. Rb2 has been identified as a P-gp substrate, and drug-mediated alteration in P-gp activity had an influence on the exposure and disposition of Rb2 [16]. In vitro, verapamil, a P-gp inhibitor, caused a significant uptake of Rb2 in L-MDR1 cells. Yan et al. [17]described that in Caco-2 and L-MDR1 cells, *Schisandra Lignans* (SLE) enhanced the exposure and declined of efflux ration of Rb2 through inhibiting the activity and expression of P-gp. In

Table 1
Pharmacokinetics of Rb2 in normal rats.

Subject	Compound	Dose	Method	C_{max} (ng/mL)	T_{max} (h)	AUC (ng·h/mL)	$T_{1/2}$ (h)	Ref.
SD rats	Rb2	50 mg/kg	gavage	400 ± 100	4.8 ± 3.5	970 ± 320	23.1 ± 3.7	[8]
	Rb2	10 mg/kg	i.v.	19810 ± 27900	0.083	200630 ± 28300	15.4 ± 3.7	
SD rats	ShenMai	10.4 mL/kg	i.v.	NA	NA	1,283,136 ± 395,609	75.4 ± 47.3	[14]
SD rats	RGE	1.5 g/kg for 7 d	gavage	10.0 ± 1.0	3.3 ± 1.2	282.8 ± 58.9	30.2 ± 5.2	[15]
		1.5 g/kg for 15 d	gavage	8.8 ± 3.6	3.0 ± 3.1	317.0 ± 145.9	68.7 ± 26.9	
SD rats	GE	120 mg/kg	gavage	330.4 ± 70.8	7.0 ± 2.0	10224 ± 1706	19.4 ± 2.9	[18]
	GE + SLE	120 ± 500 mg/kg	gavage	540.9 ± 45.0	9.5 ± 3.0	22310 ± 5273	19.0 ± 3.8	
SD rats	PQ extract	0.54 g/kg	gavage	160.1 ± 18.8	7.7 ± 0.8	1229.9 ± 99.6	13.3 ± 1.6	[67]
	PQ-AG extract	0.54 g/kg	gavage	264.1 ± 24.5	7.7 ± 0.8	1229.9 ± 99.6	15.6 ± 5.2	
SD rats	Shen-Fu	4.75 g/kg	gavage	59.7 ± 15.6	28.0 ± 6.2	3167.7 ± 700.9	19.7 ± 3.2	[68]
SD rats	Ginseng berry extract	600 mg/kg	gavage	395.0 ± 285.0	10.0 ± 2.0	376 ± 214	15.9 ± 1.4	[69]
SD rats	RGE	4 g/kg	i.v.	116.6 ± 8.6	7.7 ± 0.8	3885.6 ± 685.4	19.3 ± 6.8	[70]
SD rats	Shenfu injection	5.0 mL/kg	i.v.	NA	NA	44.4 ± 20.2	35.6 ± 30.7	[71]
SD rats	Weifuchun tablets	0.9 g/kg	gavage	263.3 ± 51.1	4.6	1668.4 ± 304.6	2.563 ± 0.78	[72]
Wistar rats	YiQiFuMai injection	5 mL/kg	i.v.	16290 ± 2150	NA	2421000 ± 46966	26.4 ± 1.2	[73]
SD rats	RGE	100 mg/kg	i.v.	10.4 ± 1.2	1.5 ± 0.2	89.6 ± 9.3	6.5 ± 1.5	[74]

AG Acorus gramineus; AUC, area under the plasma concentration-time curve; CL/F, oral clearance; Cmax, maximum drug concentration; GE, ginseng extract; i.v. intravenous injection; MRT, mean residence time; NA no available; p.o. oral administration; PQ Panax quinquefolius; RGE, red ginseng extract; SD, Sprague Dawley; Tmax, time of maximum concentration; $T_{1/2}$, half-life.

Table 2
Pharmacokinetics of Rb2 in abnormal rats, dogs and human.

Subject	Compound	Dose	Method	C_{max} (ng/mL)	T_{max} (h)	AUC (ng·h/mL)	$T_{1/2}$ (h)	Ref.
AMI rats	Dangqi Tongmai	129.6 mg/kg	gavage	21.5 ± 9.0	0.08 ± 0.01	55.0 ± 11.7	29.2 ± 9.0	[75]
Scopolamine-Treated rats	RGE	100 mg/kg	i.v.	17.2 ± 2.1	1.5 ± 0.2	90.3 ± 8.2	6.9 ± 1.2	[74]
Chronic heart failure rats	YiQiFuMai powder	543 mg/kg	i.v.	NA	NA	44106.5 ± 4117.9	30.1 ± 4.3	[76]
Chronic heart failure rats	Qiliqiangxin capsule	1.3 g/kg	i.v.	35.3 ± 9.9	1.50 ± 0.24	472.9 ± 203.3	35.9 ± 42.5	[77]
Beagle dogs	Shenmai San	0.64 g/kg	i.v.	4255 ± 567	NA	99590 ± 10755	97.6 ± 36.5	[78]
Healthy male	RGE	85 mg/d for 15 d	p.o.	1.26 ± 0.39	3.9 ± 2.5	47.12 ± 16.40	38.2 ± 20.3	[26]
Healthy male	RGE	10.4 mg/kg	p.o.	6.9 ± 2.3	4.5 ± 2.3	137.0 ± 48.8	51.2 ± 22.8	[27]

AMI acute myocardial ischemia ; AG Acorus gramineus; AUC, area under the plasma concentration-time curve; CL/F, oral clearance; Cmax, maximum drug concentration; GE, ginseng extract; i.v. intravenous injection; MRT, mean residence time; NA no available; p.o. oral administration; PQ Panax quinquefolius; RGE, red ginseng extract; SD, Sprague Dawley; Tmax, time of maximum concentration; T1/2, half-life.

rats, single administration of ginseng extract and SLE increased AUC of Rb2 for 2.18-fold from 10551 ± 1728 to 23198 ± 5566 ng h/mL and C_{max} for 1.63-fold from 330.46 ± 70.86 to 540.94 ± 45.03 ng/mL [18]. T_{max} and $t_{1/2}$ have no changed with the absence and presence of SLE. Multiple administration (for 10 continuous days) of SLE could significantly enhance the exposure of Rb2. These results indicated that SLE could enhance the exposure of Rb2 and change its pharmacokinetic properties as an inhibitor of P-gp. On the contrary, ginsenoside Rb2 had little inhibitory effect on P-gp in vitro, but its metabolites (compound k and 25-OH-PPD) could increase the intracellular accumulation of rhodamine 123 (a typical P-gp substrate). It indicated that oral administration of Rb2 may enhance the absorption of P-gp substrate drugs, due to it metabolized to compound K,25-OH-PPD and other metabolites by the intestinal bacteria [19].

Organic anion transporting polypeptide (OATP/Oatp) transporters are responsible for the uptake of various drugs in the liver, and many clinical herb-drug interactions are caused due to OATP inhibited. In the HEk293 cells overexpressing drug transporters, Rb2 demonstrated high inhibitory on OATP1B3 and OATP1B1 with the IC_{50} of 1.76 and 47.6 μM, respectively. But in rats, Rb2 had limited change on the pharmacokinetics of valsartan, an OATP substrate, following repeated oral administration of ginseng products. The lack of in vivo herb-drug interaction between Rb2 and OATP substrates could be attributed to the low plasma concentration and hepatic distribution of Rb2, which is far from the IC_{50} required for inhibiting OATP activity [20].

Some studies have attempted to evaluate the herb-drug interaction of ginseng extract and ginsenosides on cytochrome P450 (CYP). THOMAS et al. [21]reported that in vitro Panax ginseng extract (G115) decreased human recombinant CYP1A1, CYP1A2 and CYP1B1 activities, but individual Rb2 (0.66 μg/mL), equivalent to that found in an inhibitory concentration of G115, did not affect their activities. Rb2 at a high concentration of 50 μg/mL could reduce CYP1A1, CYP1A2 and CYP1B1 activities. Other studies reported that Rb2 exhibited very weak inhibitory activity on CYP3A4, CYP2D6, CYP2C19 and CYP2C9 enzymes in vitro [22–24]. These in vitro data indicated that Rb2 had negligible effects on CYP enzymes, and it was predicted to hardly alter the metabolism of drugs whose elimination is via these P450 isoforms in vivo [25].

Based on this data generated above, Rb2 was thought as a substrate of these drug transporters and CYP enzymes. We should focus on the PK alternation of Rb2 due to Rb2-drug interaction. However, Rb2 had a tiny impact on the metabolism of drugs via P-gp, OATP and P450 in vivo, partly attributed to its low plasma concentration that hardly regulated these drug transports and enzymes.

2.3. Clinical pharmacokinetics

The clinical pharmacokinetics of Rb2, mostly as part of whole ginseng extract, was investigated. One paper compared the pharmacokinetics and tolerability of Rb2 after single and repeated administration of red ginseng extract (containing 11.4 ± 0.6 mg Rb2) for 15 days in healthy volunteers [26]. The concentrations of Rb2 in plasma was stable over time, and had a long $t_{1/2}$, 38.19 ± 20.33 h and 68.99 ± 26.92 h respectively. The other pharmacokinetic parameters with single dose or repeated dose were as follows: C_{max} (1.26 ± 0.39 and 8.83 ± 3.68 ng/mL), AUC (47.12 ± 16.40 and 316.96 ± 145.92 ng h/mL), T_{max} (3.87 ± 2.47 and 3.02 ± 3.08 h). The study indicated that multiple-dose boosted the accumulation of C_{max} and AUC, but it had little impact on T_{max} and $t_{1/2}$. These results indicated that Rb2 had poor absorption and long metabolism.

Another study reported a detection method of 13 ginsenosides in human plasma after two week-repeated administration of red ginseng extract (containing 10.4 ± 1.2 mg Rb2) [27]. The key pharmacokinetic parameters of Rb2 were close to the previous study: C_{max}, T_{max}, AUC and $t_{1/2}$ were 6.9 ± 2.3 ng/mL, 4.5 ± 2.3 ng h/mL, 137.0 ± 48.8 ng h/mL and 51.2 ± 22.8 h, respectively. The study highlighted that the plasma concentration of Rb2 was stable for 4–10 h post dose, indicating stable absorption and slow elimination. The long $t_{1/2}$ also confirmed that Rb2 had a slow excretion process.

These results indicated that the preliminary pharmacokinetic properties of Rb2 in human beings were stable and reproduced. Data in Tables 1 and 2 showed that the T_{max} values of Rb2 in humans were much shorter than in normal rats. The longer half-life of Rb2 was more prominent in humans than in rats. C_{max} and AUC confirmed the poor exposure of Rb2 in two species. Such results demonstrated that Rb2 in humans had a slower absorption and longer elimination compared with rats. To make a stronger conclusion, more research including the administration of individual Rb2 and larger population size should be implemented.

In summary, Rb2 exhibits poor exposure and bioavailability in animals and humans, mainly related to poor permeability across intestinal mucosa, metabolism in the intestine, and low water-soluble. Low bioavailability greatly limits its efficacy and application, and more studies should be investigated to crack this obstacle.

3. Pharmacology of Rb2

3.1. Anti-diabetes and its complications

Type 2 diabetes (T2DM) is a disease of metabolic disorder, clinically characterized by chronic hyperglycemia [28]. Insulin

resistance (IR) is the major cause of T2DM, resulting in target cells not sensitive to insulin and blood glucose level increasing [29]. The remission of IR is a critical challenge to treat T2DM. Another important factor for the prevalence of T2DM is due to a huge increase in the population being obese or overweight [30,31]. Ginseng and ginsenoside Rb2 possess the abilities against hyperglycemic, obesity, IR and hyperlipidemia by regulating glycemic metabolism, body weight, insulin sensitivity as well as fat accumulation, which contribute to the treatment of diabetes and relevant complications.

Insulin resistance (IR) is a medical condition that the body fails to make use of insulin properly, leading to the increase of glucose level. In a study exploring the potent ability of Rb2 against IR in high fat die-induced mice (DIO), the mice administrated with 40 mg/kg Rb2 for 10 days had lower blood glucose level and higher insulin sensitivity compared with the control group [32]. More results from other studies demonstrated that Rb2 could reduce body weight, improve insulin sensitivity and glucose tolerance in animal model [33–35]. In vitro using 3T3-L1 adipocytes cells, blood glucose uptake significantly declined in a TNF-α-induced IR condition. Rb2 at treatment with 25 μM enhanced glucose uptake and attenuated TNF-α-induced IR through improving the IRS-1/PI3K/AKT insulin signaling pathway [32]. Yi Lin et al. [33] reported that Rb2 treatment could also inhibit pyroptosis of adipocytes and ameliorate IR in 3T3-L1 cells via the NF-kβ pathway. The related genes of insulin sensitivity, such as adiponectin, GLUT4 and IRS-1, had a higher expression. In addition, Luo et al. firstly found that Rb2 at 0.5 μg/mL had a significant effect of increasing insulin secretion and promoting β cell migration in vitro models of human pancreatic islets [36].

High blood glucose level is a clinical syndrome with diabetes, and Rb2 has a positive effect on glucose consumption. In the DIO mice, the treatment of Rb2 largely reduced body fat weight, improved glucose metabolism and increased energy expenditure [32,34]. In vitro, Rb2 at the concentration of 10 and 20 μM showed a strong activation on AMPK$\alpha 2\beta 1\gamma 1$, which was thought to be a promising therapeutic target for T2DM. Rb2 as a sensitive AMPK activator promoted glucose consumption in differentiated L6 myotubes [37]. On the other hand, gluconeogenesis was a physiological process to promote blood glucose increasing. Lee et al. [38] reported that in H4IIE cells, Rb2 in a dose-dependent manner attenuated the increase of glucose production stimulated by palmitate via hepatic gluconeogenesis. The molecular mechanism revealed an upregulation effect of Rb2 in the expression of AMPK and its downstream SHP (small heterodimer partner) signaling pathways, which consequently inhibited the expression of the gluconeogenic enzymes.

In terms of fat metabolism, Rb2 activated brown fat functionality and induced browning white fat, resulting in the increase of thermogenesis and energy expenditure [34]. Action mechanisms of Rb2 in alleviating hepatic lipid accumulation were studied that it could promote hepatic autophagy via silent information regulator 1 (SIRT1) induction and AMPK activation in cultured steatotic hepatocytes [34]. Another study reported the effects of Rb2 on lipid metabolism in 3T3-L1 adipocytes cultured high cholesterol conditions, in the presence of fetal bovine serum (FBS) or under fatty acid conditions [39]. In these differentiated conditions, supplements with Rb2 (10 μg/mL) all showed the ability to significantly reduce cholesterol and TAG levels ($p < 0.01$), which was comparable with the effects of lovastatin. And the mechanism of Rb2 on lipid metabolism was dependent on its stimulation effects for the expression of the sterol regulated element binding protein (SREBP) and Leptin mRNA. Meanwhile, another study also verified these effects in HepG2 cells, showing that Rb2 decreased the cholesterol level by enhancing expression of the low density lipoprotein (LDL) receptor gene through transcriptional induction of SREBP [40].

Rb2 could alleviate insulin resistance, promote insulin secretion, enhance blood glucose uptake and consumption, inhibit gluconeogenesis, activate brown fat functionality and reduce cholesterol and TAG level by regulating different pathways and molecules. All these effects are responsible for Rb2 to regulate insulin sensitive, glycemic metabolism, as well as fat accumulation. In summary, as shown in Table 3, these findings highlighted that ginsenoside Rb2 would become a potential therapeutic agent for the treatment of diabetes and its complications.

3.2. Cardioprotective effect of Ginsenoside Rb2

3.2.1. Treatment for MI/R injury

Myocardial ischemia/reperfusion (MI/R) injury is an adverse cardiovascular outcome after myocardial ischemia, cardiac surgery or circulatory arrest, resulting in arrhythmia, cardiomyocyte apoptosis and heart hypofunction [41]. Oxidative stress and the accelerated reactive oxygen species (ROS) production play key roles in the progression of MI/R, causing direct cardiomyocyte damages, myocardial remodeling and heart failure [42,43]. In animal model of MI/R injury rats, Rb2 (10 and 20 mg/kg) enhanced the activities of antioxidant enzymes, including catalas (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GSH-PX), in a dose-dependent manner and played a protection against ROS damages [44,45].

In vitro using H_2O_2-induced H9c2 cells, pretreatment of Rb2 inhibited the damages of ROS by increasing the activities of SOD and decreasing the level of lactate dehydrogenase (LDH) and malondialdehyde (MDA) [45]. These effects were consistent with another study that a mixture of Rb2 and the isomer Rb3 exerted a protection against oxidative stress and ROS damages [46]. In addition, Rb2 imposed the anti-apoptotic effects on cardiomyocytes by restoring the anti-apoptotic protein levels (Bcl-2, procaspase-3 and 9) and reducing the expression of the apoptotic molecule Bax [45].

Oxidative stress and ROS were characterized by excessive inflammatory responses, which led to necrosis and apoptosis of cardiomyocytes [47]. Treatment with Rb2 significantly reduced inflammatory cytokines levels (IL-1β, IL-6 and TNF-α) in the MI/R injury rats ($P < 0.01$) [48]. Further studies confirmed that sirtuin-1 (SIRT1) was a mediator to decrease oxidative stress, ROS and pro-inflammatory cytokines, and Rb2 could upregulate the expression of SIRT1 and play a protective role in the MI/R injury [48–50].

3.2.2. Treatment for atherosclerosis

Inflammatory response was important risk factors in the pathogenesis of atherosclerosis [51]. In LPS-treated HUVECs and THP-1 myocytes cell lines, treatment with Rb2 (20 μM) alleviated inflammatory responses by downregulating the phosphorylation of NF-κB and the release of TNF-α and MCP-1 in a dose-dependent manner [52]. However, ROS level had no change after the treatment with Rb2. This finding was linked with the upregulation mechanism of Rb2 on the expression of GPR120/AMPK/HO-1 signaling in HUVECs. In another study, Rb2 showed a similar impact on inflammation by regulating GPR120 signaling in LPS-stimulated mouse macrophage RAW264.7 cells [53].

The above results indicated Rb2 had good cardioprotective effects by inhibiting oxidative stress, ROS and inflammatory responses. Rb2 could be developed into a potent drug for heart diseases.

Table 3
Anti-diabetes and its complications of Rb2.

Model	Type	Animal/Cell	Description	Ref.
T2DM Obesity	In vivo	Male C57BL/6 J mice	Ameliorating IR, reduced body weight and improving glucose metabolism	[32]
	In vitro	3T3-L1 adipocytes	Ameliorating IR through phosphorylation of AKT and MAPK pathways	
Obesity DM	In vivo	Male C57BL/6 J mice	Ameliorating IR in HFD-fed mice by reducing cell pyroptosis	[33]
	In vitro	3T3-L1 adipocytes	Ameliorating IR via the inhibition of inhibiting pyroptosis through the NF-kβ pathways	
Obesity	In vivo	Male C57BL/6 J mice	Activating brown fat functionality, induced browning of white fat, and consequently increasing thermogenesis and energy expenditure	[34]
	In vitro	3T3-L1 adipocytes	Activating AMPK through its downstream PGC-1a and UCP1 genes	
Obesity NAFLD	In vivo	db/db mice	Preventing hepatic lipid accumulation by promoting autophagic through both the SIRT1 and AMPK pathways	[35]
	In vitro	HepG2 cells	Restoring Autophagy and attenuating lipid accumulation mostly through AMPK activation and SIRT1 induction	
DM	In vitro	human pancreatic β cells and islet tissue	Promoting insulin secretion and stimulating islet migration and reconstitution	[36]
T2DM	In vitro	L6 myotubes	Promoting the glucose consumption and activating AMPKα2β1γ1	[37]
T2DM	In vitro	H4IIE cell	Increasing SHP expression and inhibiting gluconeogenesis via AMPK signaling.	[38]
HC	In vitro	3T3-L1 adipocytes	Lowering TAG levels by stimulating the expression of SREBP and Leptin mRNA	[39]
Lipid disorder	In vitro	HepG2 cells	Decreasing the cholesterol level by enhancing expression of the low density lipoprotein (LDL) receptor gene through transcriptional induction of SREBP	[40]

AMPK Adenosine 5'-monophosphate (AMP)-activated protein kinase; AKT protein kinase B; DM, diabetes mellitus; HC hypercholesterolemia; HFD, high-fat diet; IR, insulin resistance; MAPK, mitogen activated protein kinase; NAFLD nonalcoholic fatty liver disease; NF-kβ nuclear factor kappa-B; OA high glucose; PGC-1a peroxlsome proliferator-activated receptor-γ coactlvator-1α; SHP small heterodimer partner SREBP Sterol-regulatory element binding proteins SIRT1 silent information regulator 1; TAG triacylglycerol; T2DM, type 2 diabetes; TNF-α, tumor necrosis factor-α; UCP-1 uncoupling protein.

3.3. Anti-osteoporosis

An in vivo and in vitro study reported anti-osteoporosis potency of Rb2. ROS and oxidative damage would inhibit osteoblast differentiation and enhance bone resorption, resulting in the progression of osteoporosis. In ovariectomized mice, Rb2 administration for 12 weeks partly inhibited serum oxidative damage and rescued antioxidant enzyme activities, such as malondialdehyde (MDA) and glutathione (GSH). Moreover, Rb2 improved trabecular microarchitecture and bone mass in mice [19]. In vitro, treatment of Rb2 (0.1–10 μM) dose-dependently protected osteoblastic MC3T3-E1 cells against osteoblast dysfunction and oxidative damage through reducing the level of ROS and bone-resorbing cytokines [19]. Bo et al. [54] found the anti-apoptotic effect of Rb2 on Bone Marrow-Derived Mesenchymal Stem Cells (BMMSCs), which had a direct inhibitory impact on osteoporosis. The molecular mechanism showed that Rb2 reversed Dex-induced apoptosis and improved the cell viability by activating the GPR120/Ras/Erk1/2 cascade in BMMSCES. Another study demonstrated the inhibitory effects of Rb2 on osteoclast differentiation and bone resorption activity. This mechanism was associated with blocking NF-kB and STAT3 signaling pathways [55]. In summary, Rb2 displayed protective effects against osteoporosis by regulating the differentiation of osteoblast and osteoclast, and it was a promising agent for the treatment of osteoporosis.

3.4. Anti-cancer

The anti-carcinogenic properties of Rb2 on colorectal have been reported in several studies. The paper reported that the tumor growth and volume of mice were significantly inhibited in the Rb2 treatment group than the control group [57]. Intraperitoneal administration of Rb2 (5 mg/kg) significantly suppressed the metastasis of colorectal cancer cells in a mouse mode of metastasis ($p < 0.05$) [56]. Studies also determined the anti-tumor effects of Rb2 in the colorectal cancer cell lines HCT116, HT29 and SW620, inhibiting the growth, migration, invasion and wound healing of colorectal cancer cells [56,57]. The study found that Rb2 decreased the expression of Epithelial-mesenchymal transition (EMT) and cancer stem cells via the downregulation of EGFR/SOX2 signaling [57]. Another study verified the inhibitory mechanism of Rb2 against EMT through downregulating the TGF-β1/Smad signaling in vivo and in vitro.

In the research of anti-lung cancer, multiple administrations of Rb2 significantly inhibited the lung metastasis, produced by B16-BL6 cells, in a time-dependent manner in mice. The possible mechanism was partly due to the inhibition of tumor-associated angiogenesis by Rb2, and its underlying mechanism still needs to be investigated [58].

3.5. Anti-UV

Only a few studies have reported the anti-photoaging effect of Rb2. The ultraviolet (UV) could induce the production of ROS and disrupt the antioxidant ability of skin, and sequentially cause skin photoaging and other skin diseases. Pretreatment with Rb2 obviously reduced the UV-B-induced ROS enhancement in a dose-dependent manner in human dermal keratinocytes and fibroblasts [59–61]. The expression of matrix metalloproteinase-2 (MMP-2) contributed to the process of photoaging, and the study found that Rb2 could suppress its expression and activity [60]. The mechanism experiments found that the effects on anti-photoaging were achieved by increasing the depleted GSH and SOD activity, which could decrease ROS level and MMP-2 expression [59,60]. It suggested that Rb2 may be a potential candidate for the treatment of skin photoaging.

3.6. Neuroprotective effects

Ginsenosides possess the ability to protect neurons and improve cognition under different pathological conditions [62,63]. In HT22 murine hippocampal neuronal cells, the neuroprotective capability of a serials of ginsenosides (Rb1, Rb2, Rc, Rd, Rg1 and Rg3) was investigated, and Rb2 showed stronger effects on the cell viability compared with others [64]. The further assay identified that glumtamate-induced cytotoxicity and the excessive production of intracellular ROS were significantly suppressed by Rb2 with a concentration of 25.7 μm. And in vivo using ischemic brain injury animal model, administration of 10 mg/kg Rb2 significantly decreased the number of degenerated neurons. The

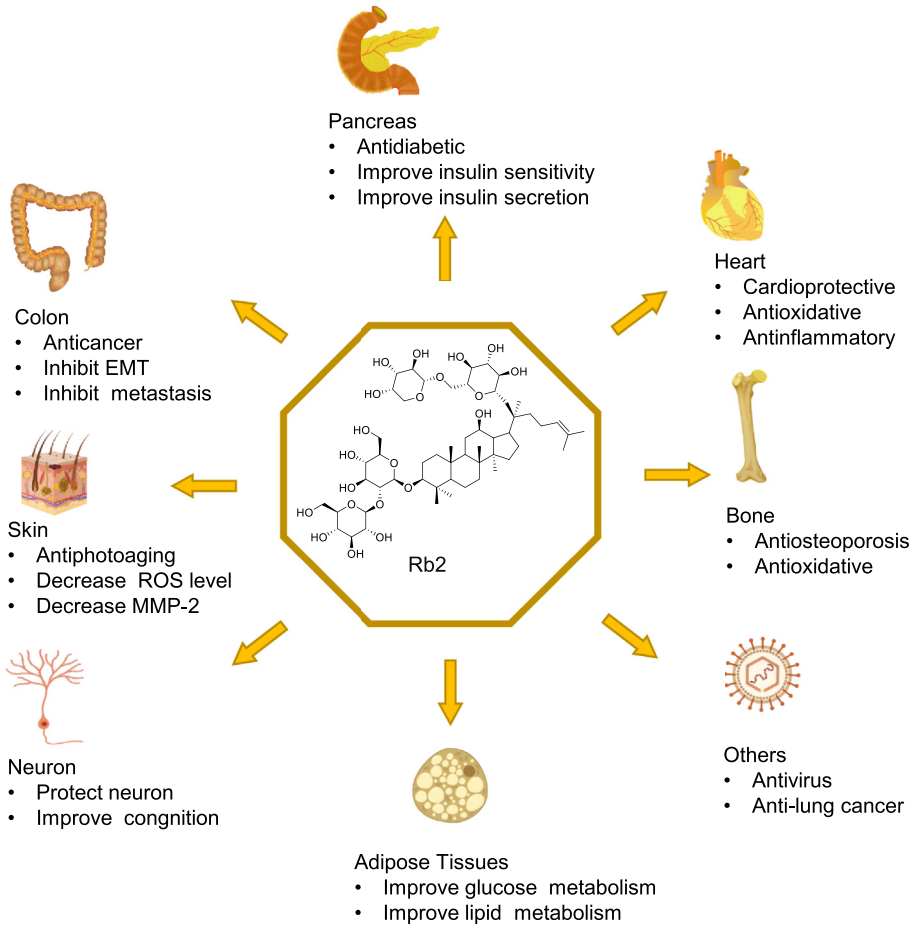

Fig. 2. Therapeutic effects of ginsenoside Rb2 in different systems and/or tissues.

neuroprotective effects of Rb2 were thought to be due to the up-regulation of antiapoptotic Bcl-2 and downregulation of pro-apoptotic Bax and MAPKs.

3.7. *Anti-virus*

It is reported that ginseng and ginsenosides have preventive effects on virus infection, such as H1N1, H1N2, murine norovirus and feline calicivirus. The protective abilities of ginsenosides (Rb1, Rb2, Rd, Re, Ro and Rg2) against the lethal infection of haemagglutinating virus of Japan (HVJ) in mice were studied, and pretreatment of Rb2 showed the highest potency with a 71.4% survival rate [65]. The protective mechanism of Rb2 was involved in the enhancement of mucosal immunity and the suppression of HVJ virus growth in HVJ-infectious mice. In the newborn mice of rotavirus infection, prtreatment of Rb2 reduced virus titers and RV-induced diarrhea in a dose-dependent and time-dependent manner [66]. These results meant that Rb2 was a promising candidate as an antiviral reagent to prevent infection.

4. Conclusion

The review focused on the current content concerning the source, pharmacokinetics and pharmacology of Rb2. Accumulating evidence has proved beneficial effects of Rb2 on many diseases in vitro and animal models (Fig. 2), including anti-diabetes, anti-obesity, anti-inflammation, anti-oxidation, anti-virus, anti-tumor and effects on the cardiovascular system. The diverse bioactivities were attributed to the regulation of Rb2 on the signaling pathways and molecules, such as AKT/SHP, MAPK, EGFR/SOX2, TGF-β1/Smad, SIRT1, GPR120/AMPK/HO-1 and NF-κB. In particular, the paper outlined the anti-diabetic potency of Rb2 through multi-effects, multi-targets and multi-pathways, which provided a potential lead drug for the treatment of diabetes and its complications.

The PK profiles of Rb2 exhibit poor oral absorption and bioavailability that restricts its efficacy and clinical use. More strategies for overcoming its poor absorption are urgent, such as new drug delivery systems, chemical modification and so on. In the aspect of pharmacology, some specific mechanisms have not yet been fully elucidated. For example, Rb2 inhibited the metastasis of tumor in lung cancer, but its regulatory mechanism is not clear. In anti-UV, neuroprotection and anti-virus, there is a lack of more deep and systemic investigations. The currently available results are mainly collected from in vitro cell culture experiments and in vivo rodent models, and further investigations should concentrate on how to do more research in clinical.

In this paper, we have tried to elucidate the pharmacokinetic and pharmacological profiles of Rb2, and these findings could provide a reference for the development of Rb2 as a promising drug.

Declaration of competing interest

The author declares no conflicts of interest.

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