

# A mini-review on pharmacological effects of ginsenoside Rb3, a marked saponin from *Panax genus*

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**Key words:** Ginsenoside Rb3, Pharmacological effects, Review, Signaling pathway

**Abstract:** Ginsenoside Rb3 (G-Rb3) is one of the primary active compounds isolated from *Panax ginseng* Meyer, which belongs to protopanaxadiol ginsenosides (PPD). Based on the structure-activity relationship (SAR) of ginsenosides, the pentose structure of G-Rb3 limited itself to possess more pharmacological activity to a certain extent. However, pharmacokinetics show that G-Rb3 is processed through deglycosylation in the intestinal tract and converted into more active rare saponins, such as Compound K, F2, etc. A series of studies focused on neuroprotection and the cardiovascular system demonstrating its therapeutic potentials, which was achieved by diminishing oxidative stress and apoptosis. Therefore, more systematic and in-depth studies are needed to complete the pharmaceutical value and to promote its clinical applications. This article highlights the multiple pharmacological effects and mechanisms of G-Rb3 and prospects for its development.

## List of Abbreviations

**AUC:** area under the plasma concentration vs. time curve;  
**MRT:** mean residence time;  
**T<sub>max</sub>, t<sub>1/2</sub>:** the elimination half-life.

## Introduction

Ginseng, a highly valuable and special medicinal herb, has been proposed to be an adaptogen over 2000 years in China (Chen *et al.*, 2008; Gao *et al.*, 2016). The cognition of its “homology of medicine and food” was promoted and recognized in China, Korea, Japan, Europe, and America. Belonging to the Araliaceae family, ginseng is a perennial medicinal plant, mainly growing in the East Asia region, especially in cold zones. Evidence demonstrated that ginsenosides contribute primarily to the pharmacological function of ginseng (Choi, 2008), such as anti-tumors (Xia *et al.*, 2014), anti-inflammatory (Chen *et al.*, 2007; Liu *et al.*, 2020a), antifatigue (Tang *et al.*, 2008), etc. Among the series of ginsenoside candidates, researchers have suggested that G-Rb3 could be potential substitute medicines for diverse

diseases, including not limited to anti-inflammatory (He *et al.*, 2014), anti-diabetic (Bu *et al.*, 2012), and antioxidant (Shi *et al.*, 2011), but also neural (Cui *et al.*, 2012) and cardiovascular protective effects (Shi *et al.*, 2011).

As mentioned the pharmacological activity of ginsenoside, it is natural to explain its related structure-activity relationship (SAR), in which the position and number of sugars in ginsenoside determine their pharmacological activity (Wang *et al.*, 2007). For example, the rare ginsenoside Rg3 is formed with special functions after being metabolized in the body owing to its crucial transformation in sugar. Different from Rg3, G-Rb3 is relatively richer in ginseng rhizomes, and mainly derived from *Panax notoginseng*/P. *quinquefolius* L./P. *ginseng* Meyer/ *Gynostemma pentaphyllum* (Thunb.) Makino/P. *japonicus* C. A. Mey (Jia *et al.*, 2019; Liu *et al.*, 2018; Zhang *et al.*, 2021; Zhang *et al.*, 2019). For SAR, although G-Rb3 shows potentials for the prevention of neurological and cardiovascular diseases, the pentose structure (3 sugars) of G-Rb3 limits itself from possessing more pharmacological activity to a certain extent. Hence reviewing and summarizing research achievements on Rb3 contribute to its further application in clinical.

## Chemical Features of G-Rb3

According to the different structures of aglycones, ginsenosides can be divided into three types: Dammarane (including

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Received: 24 May 2021; Accepted: 07 July 2021



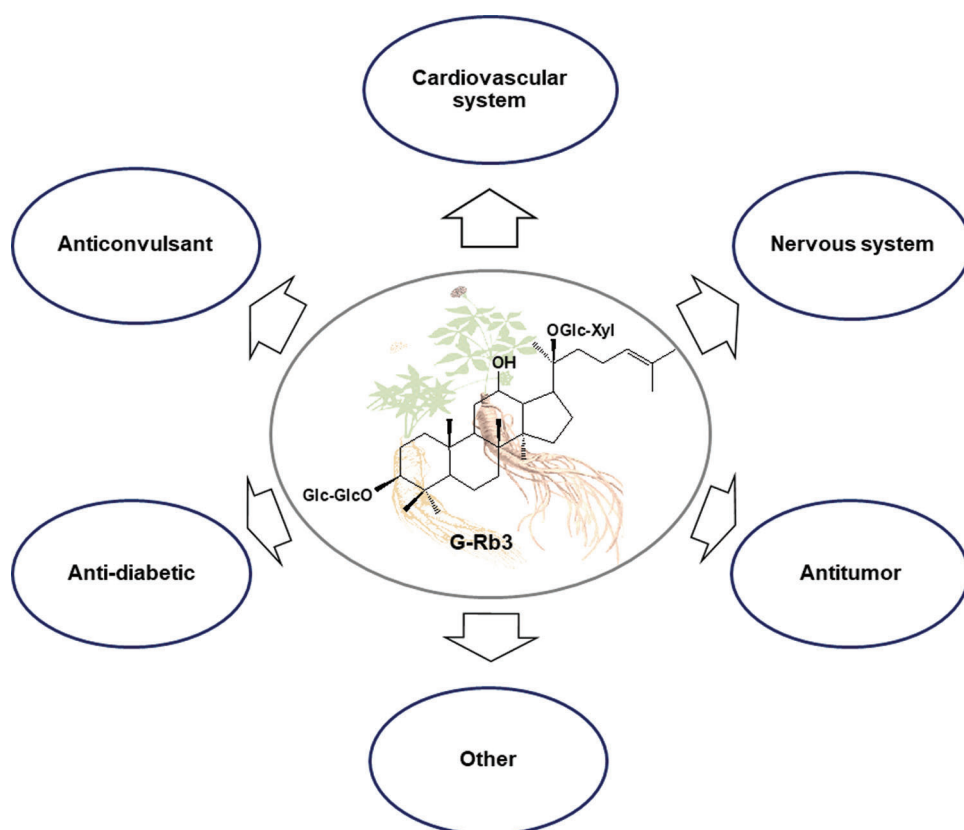


FIGURE 1. Summary of various pharmacological activities related to G-Rb3.

Topazanediol and Topazanetriol), Oleanose, and Ocorol. G-Rb3 is a type of tetracyclic triterpenoid saponin, belongs to PPD. G-Rb3 possesses 1 xylose and 3 glucose moieties with 20(S)-protopanaxadiol (PPD) aglycone (Fig. 1), which is one of the major ginsenosides with a content of about 2.1 mg/g in *P. ginseng* Meyer (Liu et al., 2016). The molecular formula of G-Rb3 is  $C_{53}H_{90}O_{22}$ , with a molecular weight of 1079.2844 g/mol. It is white powder and soluble in water, methanol, and ethanol. It was found that the content distribution order of G-Rb3 was *Panax notoginseng* > *P. quinquefolius* L. > *P. ginseng* Meyer > *Gynostemma pentaphyllum* (Thunb.) Makino > *P. japonicus* C. A. Mey. Recent studies revealed that the type of dammarane, the number of sugar moieties, and differences in the substituent groups were responsible for its anti-cancer effect owing to its biological SAR (Liu et al., 2003; Wang et al., 2007). Herein, we hypothesize that the structure of G-Rb3 (1 xylose and 3 glucose moieties) may affect its relevant pharmacological activities.

### Pharmacokinetic Studies on G-Rb3

Understanding the pharmacokinetics of ginsenosides is crucial for designing an optimal dose regimen and avoiding the potential unwanted interactions between ginsenosides and other drugs in clinical application. It is logical to think that the pharmacokinetic behaviors of ginsenosides are based on molecular structures. However, G-Rb3 with one glucose-linked  $\beta$ -D-xylose is poorly absorbed than G-Rb1 by the oral administration tracked using liquid chromatography-tandem mass spectrometry (LC-MS<sup>n</sup>) analysis (Zhao et al., 2012) which may be attributed to its pentose groups. Pharmacokinetic parameters of G-Rb3 are shown in Table 1.

Comparatively, the elimination of i.v. is faster than p.o. The lengths of the ginsenoside sugar chain are closely but negatively related to their biological activities (Park et al., 2010; Tawab et al., 2003). Further study demonstrated that deglycosylation was the major metabolic pathway of G-Rb3 in rats, and the mean plasma elimination half-lives for distribution and exterminate phases  $t_{1/2\alpha}$  and  $t_{1/2\beta}$  were  $13.77 \pm 1.23$  min and  $2045.70 \pm 156.20$  min (Zhao et al., 2018). Meanwhile, two major metabolites Mb1 and M2' were tentatively identified in rat urine samples after intravenous administration, and the additional two metabolites were F2 and CK after oral administration, as depicted in Table 2. In summary, it is urgent to identify the effective delivery pathway of G-Rb3.

It is commonly accepted that orally ingested major ginsenosides (such as Rb1, Rb2, and Rb3), containing three to five sugars of these saponins, can be deglycosylated into active minor ginsenosides, also named "rare ginsenoside", by the intestinal bacteria of the microflora. More specifically,

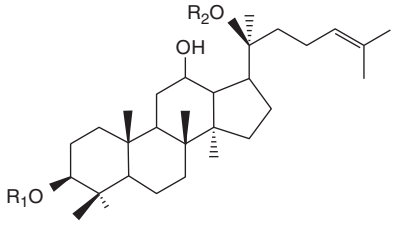
TABLE 1

Pharmacokinetic parameters of Rb3 after i.v. (10 mg/kg) and oral (50 mg/kg) administration in rats

Pharmacokinetic parameters	i.v.	p.o.
$AUC_{0-t}$ (mg h/L)	$1437.0 \pm 108.6$	$37.4 \pm 20.2$
$AUC_{0-\infty}$ (mg h/L)	$2229.9 \pm 684.6$	$55.1 \pm 29.4$
$t_{1/2}$ (h)	$24.9 \pm 12.6$	$21.1 \pm 9.8$
$MRT_{0-t}$ (h)	$13.4 \pm 0.5$	$13.9 \pm 3.8$
$T_{max}$ (h)	0.083	$1.5 \pm 2.0$
$C_{max}$ (mg h/L)	$160.9 \pm 31.6$	$3.3 \pm 1.9$

TABLE 2

Structures of ginsenosides and metabolites (Glc: glucose, xyl: xylose)



Compound	R1	R2
Ginsenoside Rb3	Glc2-Glc	Glc6-xyl
Ginsenoside Mb1	Glc	Glc6-xyl
Ginsenoside M5(F2)	Glc	Glc
Ginsenoside M2'	H	Glc6-xyl
Ginsenoside M1(C-K)	H	Glc

major ginsenosides may act as pro-drugs when they are taken orally, and their deglycosylated derivatives are responsible for the *in vivo* effects. Given the biotransformation of G-Rb3, enzymology studies were performed to prepare rare ginsenosides through G-Rb3 (Liu *et al.*, 2014a).

### Pharmacological Properties

*Protective effects for nervous system and possible mechanisms*  
According to pretreatment or posttreatment of G-Rb3 in different experimental reports, the potential effect of G-Rb3 on the central nervous system injury model is mainly aimed at hypoxic/ischemia brain injury and oxygen and glucose deprivation (OGD) stress. G-Rb3 has been proven to possess a neuroprotective effect on various cell lines *in vitro* and several animal models *in vivo* through multiple molecular mechanisms (Fig. 1).

In a cultured hippocampal neurons model tested with hypoxia, G-Rb3 stabilized the cell membrane and suppressed NOS, especially inducible nitric oxide synthase (iNOS) (Shen *et al.*, 2006a). In glutamate-treated hippocampal neurons, G-Rb3 enhanced the hippocampal neuronal viability, decreased the lactate dehydrogenase (LDH) leakage, and elevated the nitric oxide synthase (eNOS). A report has provided vital evidence that G-Rb3 exhibits significant protective effects on glutamate excitotoxic injury (Shen *et al.*, 2006b). The involved mechanism may include antagonizing the injury of neuron membrane, inhibiting the viability of iNOS, and increasing the activity of eNOS.

In further research related to OGD, the anti-ischemic activity of G-Rb3 was confirmed in ischemic and reperfusion injury model of PC12 cells by increasing cell viability, Bcl-2 protein expression and inhibiting LDH release, activities of cytosolic cytochrome c, cleaved-caspase 3, caspase-3, -8, -9 and Bax protein expression. The related mechanisms, at least partly, may be attributed to the effect of G-Rb3 to suppress the intracellular  $Ca^{2+}$  elevation and inhibiting mitochondria-mediated apoptosis pathway (Zhu *et al.*, 2010).

Another study by Xu *et al.* (2005) showed that G-Rb3 inhibited strychnine-sensitive glycine receptors in acutely dissociated hippocampal neurons of rats. The GABA<sub>A</sub> receptor, a ligand-gated ion channel consisting of the chloride channel complex, activation increases the membrane conductance which further suppresses postsynaptic action potential discharge accompanied by blocked excitatory synaptic responses (Leidenheimer, 2008; Zhou *et al.*, 2007). G-Rb3 exhibits neuroprotection via modulating GABA<sub>A</sub> receptor in the OGD model *in vitro* (Jiang *et al.*, 2011). In addition to this receptor, the neuroprotective activity of G-Rb3 was reported through the inhibitory action on the NMDA receptor (Jiang *et al.*, 2018). In NMDA receptor-treated rat hippocampal neurons cells, neuronal viability was reduced accompanied by the leakage of LDH and  $Ca^{2+}$  influx (Berliocchi *et al.*, 2005; White *et al.*, 2000). Nevertheless, NMDA receptor activation caused excitotoxicity can be reversed by the treatment of G-Rb3. The underlying protective mechanisms of G-Rb3 may attribute to inhibiting NMDA receptors induced by the acceleration of concentration-dependent  $Ca^{2+}$  levels accompanied with the reduced intracellular free  $Ca^{2+}$  in the pathological response of hypoxic/ischemic brain injury (Peng *et al.*, 2009). Early studies (Cui *et al.*, 2012) on G-Rb3 showed a protective effect against ischemic neurons, which might be achieved through the suppression of persistent  $Na^+$  by NMDA triggered imputation of  $Ca^{2+}$  levels (Peng *et al.*, 2009) *in vitro*.

Further data in SK-N-SH cells suggest that G-Rb3 possesses a dammarane-type core structure, which may be responsible for its significant effect in promoting neurite outgrowth activity (Zou *et al.*, 2002). Nevertheless, the underlying mechanism of G-Rb3 has not been fully elucidated. Additional evidence of a neuroprotective effect of G-Rb3 has been obtained in a rat neuro-damaging model induced by 3-nitropropionic acid (Lian *et al.*, 2005a). The protective mechanism of G-Rb3 may attribute to preventing ischemia and hypoxia sodium channel allosteric, scavenging oxygen free radicals, inhibiting lipid peroxidation, antagonizing calcium ions, and reducing the neurotoxicity of glutamate and nitric oxide (NO).

Depression is a common mental disorder in the clinic. The prevention and treatment of depression have been sought by the medical profession and society (Bebbington, 2001). G-Rb3 exhibits antidepressant-like activity *via* regulating multiple signaling pathways and targets. A study by Cui *et al.* (2012) showed that G-Rb3 was shown to alleviate hypothermia, palpebral ptosis, and immobility in a reserpine-induced syndrome model; they further revealed that chronic G-Rb3 treatment increased the locomotor activity, food consumption, and restored sucrose preference in the chronic mild stress model (Cui *et al.*, 2012), indicating that G-Rb3 produce antidepressant-like activity by involving the function of noradrenergic pathways. Another study demonstrated that treatment with G-Rb3 (10, 50 mg/kg) remarkably increased the level of mouse brain monoamine neurotransmitters (NA) *via* regulating noradrenergic pathways (Zhang *et al.*, 2016). Additionally, the protective effects on the nervous system are also important, such as the regulation of neurotrophic factor expression in the nervous system.

### Protective Effects on Cardiovascular System and Possible Mechanisms

It is worth noting that accumulating sights have been focused on the research relevant to ginseng on cardiovascular diseases, especially in protopanaxadiol. According to the hemodynamic index in rats, G-Rb3 has a cardiovascular protective effect, which was initially proved to be related to calcium channel blockade and anti-free-radicals (Chen *et al.*, 1994; Zhong *et al.*, 1995). G-Rb3 can prevent isoproterenol-induced cardiovascular damage and cardiac dysfunction. *Ex vivo* G-Rb3 treatment restored Ang II-stimulated endothelial dysfunction by reversing over-expression of NADPH oxidases, NOX-2 and NOX-4 levels, over-production of reactive oxygen species (ROS), and improving NO bioavailability (Wang *et al.*, 2014). G-Rb3 suppressed angiotensin II (Ang II)-stimulated proliferation of vascular smooth muscle cells and inhibited experimentally induced myocardial dysfunction (Wang *et al.*, 2010b; Wong *et al.*, 2010). G-Rb3 administration significantly reduced the increased creatine kinase (CRE), LDH, and malondialdehyde (MDA), whereas restored the decreased superoxide dismutase (SOD) and catalase (CAT); suggesting that G-Rb3 might subdue oxygen free radical impairment and protect the antioxidant enzyme activity in cardiomyocytes (Wang *et al.*, 2010a). During acute myocardial infarction (AMI), the main damage to myocardial tissue is caused by initial ischemia and subsequent reperfusion. The beneficial effect of G-Rb3 on myocardial ischemia-reperfusion injury (MIRI) was characterized by the decrease in plasma endothelin and Ang II levels and myocardial infarct size. The underlying mechanism was in part related to its antioxidant activity and functional microcirculatory improvement. Previous studies further revealed a novel mechanism of G-Rb3 to attenuates oxidative stress *via* activating the antioxidation signaling pathway of PERK/Nrf2/HMOX1 *in vivo* and *in vitro* (Sun *et al.*, 2019). A similar study by Liu *et al.* (2014b) also confirmed that G-Rb3 administration (20 mg/kg) effectively attenuated MIRI-induced apoptosis and inflammation *in vitro*, accompanied by inhibition of B-cell lymphoma 2-associated X protein (BAX), ROS accumulation, oxidative stress, and elevated the level of B-cell lymphoma 2 (Bcl-2), an anti-apoptotic signaling. G-Rb3 regulated energy metabolism *via* activating the PPAR $\alpha$  signaling pathway, which increased expressions of key enzymes involved in  $\beta$ -oxidation of fatty acids, exerting an anti-apoptosis effect (Chen *et al.*, 2019). Liu *et al.* (2020b) also clarified the anti-apoptosis effect of G-Rb3 in myocardial ischemia-reperfusion injury. In another report using H9c2 cells subjecting to OGD followed by reperfusion (OGD-Rep), G-Rb3 suppressed the expression of NF- $\kappa$ B, phosphorylation of JNK, and many inflammatory cytokine releases, such as IL-6, TNF- $\alpha$ , monocyte chemotactic protein-1 (MCP-1), matrix metalloproteinase-2 (MMP-2) and MMP-9. This finding revealed the potential mechanism of the protective effect of G-Rb3 being attributed to the inhibition of the JNK-mediated NF- $\kappa$ B pathway (Ma *et al.*, 2014). In another myocardial injury model by Yang *et al.* (2017) pretreatment with G-Rb3 was found to improve the cell viability and further inhibit endothelial-to-mesenchymal transition (EMT) caused by coxsackievirus B3 (CVB3) through the Pyk2-PI3K-AKT pathway, in the treatment of myocardial fibrosis (MF) *in vitro*. Above all, G-Rb3 may protect cardiomyocytes from damages through signaling pathways of

inflammatory and cell proliferation, indicating that G-Rb3 may be a promising therapeutic drug to treat cardiovascular diseases. However, the establishment of a cardiovascular disease model to simultaneously track the protective effect of the drug in cardiac and vascular dysfunctions would be of great significance. By further elucidating the role of oxidative stress, apoptosis, and inflammation in the development of disease, clear guidance for the clinical application may be created accordingly.

### Antitumor Effect

Within the strategies for tumor treatment, the ability of drugs to inhibit tumor cells is usually investigated initially. The co-treatment of G-Rb3 and cisplatin enhanced tumoricidal with anti-proliferative action on human breast carcinoma MCF-7 cells. Therefore, combinations of G-Rb3 and chemotherapeutic agents may be a novel neoadjuvant agent in clinical cancer treatment (Aung *et al.*, 2007). Another similar research by Huang *et al.* (2017) demonstrated that G-Rb3 treatment in mice diminished colorectal cancer-induced increase in expression of cancer-promoting signaling and pro-inflammatory markers.

### Anti-Diabetic Effect and Possible Mechanisms

Diabetes is a metabolic disease with hyperglycemia attributed to the development of insulin-secreting or functional defects in all ages. Chronic hyperglycemia in diabetes mellitus leads to chronic impairment and dysfunction of various tissues, especially kidneys, heart, and nerves (Akkati *et al.*, 2011). Early studies suggested that G-Rb3 may act as a potential therapeutic reagent in diabetic healing. Evidence obtained from *in vitro* and *in vivo* studies demonstrated that G-Rb3 treatment significantly decreased the level of postprandial blood glucose, reinstated oral glucose tolerance at a dose-dependent manner in the normoglycemic group and mice suffered from alloxan injection, and stimulated glucose consumption in the C2C12 myotubes (Bu *et al.*, 2012).

Gluconeogenesis, the increase in liver glucose production, is an important factor in the progression of glucose disease. In physiological conditions, liver glycogen synthesis and gluconeogenesis remain in a dynamic equilibrium. However, when insulin resistance occurs in the liver, liver gluconeogenesis increases, and liver glycogen synthesis decreases. After the balance between gluconeogenesis and glycogen synthesis is disrupted, liver glycogen output increases, and then blood sugar rises. As a key regulator of energy metabolism, AMPK can reduce plasma and liver triglyceride levels and gluconeogenesis gene transcription (Cool *et al.*, 2006). Forkhead transcription factor 1 (FOXO1) is another important factor in gluconeogenesis. AMPK can regulate FOXO1, which inhibiting liver gluconeogenesis (Zhang *et al.*, 2009). G-Rb3, as an AMP-activated protein kinase (AMPK) activator, offers a promising clinical therapy for treating diabetes mellitus and its complications. Potential key targets, such as phosphoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphatase, forkhead transcription

factor 1 (FOXO1), and hepatic nuclear receptor 4 $\alpha$  (HNF4 $\alpha$ ), have been explored (Meng *et al.*, 2017).

### Anticonvulsant Effect

The possibility that ginseng may have anticonvulsant activity was first suggested by Lee *et al.* (2002). Further, the underlying anticonvulsant activity of pretreatment with G-Rb3 has been studied on different chemicals causing convulsion, including kainic acid, pilocarpine, and pentylenetetrazol in rats. However, the involved mechanism for anticonvulsant action of G-Rb3 remains unclear (Lian *et al.*, 2006; Lian *et al.*, 2005b).

### Other Pharmacological Effects

Beyond all, G-Rb3 presented obvious renal protection against cisplatin-induced renal injury through the intervention of increased ROS levels and decreased expressions of autophagy-related proteins (Xing *et al.*, 2019). In UV-B radiation-induced photogate cells, the restorative activity of pretreated G-Rb3 has been proved by the reduced levels of ROS, pro-MMP-2, and proMMP-9, the increased total glutathione (GSH) content, SOD activity, and cell viability (Oh *et al.*, 2015). In the MMPs-induced cartilage degradation model, treatment with G-Rb3 (100  $\mu$ g/mL) significantly reduced MMP3 secretion compared to S12 murine articular cartilage cells treated with IL-1 $\beta$ , indicating that G-Rb3 offered a potential therapeutic approach for the modulation of collagen degradation (Shin *et al.*, 2009). In another *in vitro* study, as an NF- $\kappa$ B inhibitor, G-Rb3 exerted anti-inflammatory activity through NF- $\kappa$ B deactivation (He *et al.*, 2014). Furthermore, the authors of this study confirmed that G-Rb3 suppressed the expression of cyclooxygenase-2 (COX-2) and iNOS messenger ribonucleic acid (mRNA) in HepG2 cells exposure to TNF- $\alpha$ , suggesting a potential role of the inflammatory response (He *et al.*, 2014). In 2, 2 V-azobis (2-amidinopropane hydrochloride) (APPH)-treated peroxidation of human erythrocytes, antioxidative properties of G-Rb3 are responsible for erythrocytes protection. However, the antioxidative mechanism of ginsenosides Rb3 in AAPH-induced hemolysis requires further study (Liu *et al.*, 2002). A similar report by Li and Liu (2008) also demonstrated that G-Rb3 protected human erythrocytes against hemin-induced hemolysis.

### Summary and Perspectives

This review first illuminates the chemical structure of G-Rb3 and then elucidates the pleiotropic protective role played by G-Rb3 in diversified diseases threatening human life. It aims to stimulate more preclinical investigations and studies on various molecular pathways employed by G-Rb3. Modern pharmacological studies have also validated intricate officinal uses of G-Rb3, though data regarding many aspects of the ginsenoside monomer, such as the mechanism of action, adverse effects, and toxicology research are still confined. Despite recent advances in nervous and cardiovascular systems, the exploration concentrated on other biological effects remains limited. Moreover, the pathways of G-Rb3 absorption, distribution, metabolism, and excretion need to

be clarified by pharmacokinetic study with multifarious drug delivery. For existing research, one factor responsible for the poor *in vivo* bioavailability of G-Rb3 may be the sugar groups. In comparison to pentose groups in G-Rb3 ginsenosides, hexose and hydroxyl groups (Rb1) in the same glycosylation site may present better oral absorption.

Taken together, based on a broad perspective in nervous and cardiovascular systems, G-Rb3 may provide substitute treatment in further theoretical study and clinical application to ascertain the effective doses. Nevertheless, it is noteworthy that the accuracy and systematisms of both *in vivo* and *in vitro* models of various diseases are not yet definitive. Therefore, more detailed emerging studies need to be taken in the transition to clinical trials. In addition, available data on G-Rb3 are still limited and perplexed. (1) Differences exist in the chemical configuration of panaxadiol saponins (PDS). Is there a different function of G-Rb3 in targeted organs, tissues, cells, or intracellular parts? (2) Does the diverse structure require a specific drug delivery? Further investigations in pharmacological action/mechanism relationship and pharmacokinetics studies are highly recommended to provide more solid evidence for the multiple effective efficiency of G-Rb3.

**Author Contribution:** Mei-ling Fan and Zi Wang conceived the idea of the whole article and provided specific guidance; Yue-yang Duan and Xiao-tong Yan completed the literature search and collation of the chemistry section; Xiang-xiang Liu and Wei Li completed a compilation of pharmacological research literature, and Wei Li is responsible for compiling of the whole work.

**Funding Statement:** This work was funded by the grant of Jilin Science & Technology Development Plan (No. 20200301037RQ).

**Conflicts of Interest:** The authors declare that they have no conflicts of interest to report regarding the present study.

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