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Review

Ginsenoside Rb_1 in cardiovascular and cerebrovascular diseases: A review of therapeutic potentials and molecular mechanisms

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ABSTRACT

Cardiovascular and cerebrovascular diseases (CCVDs), which are circulatory system diseases caused by heart defects and vascular diseases, are the major noncommunicable diseases affecting global public health. With the improvement of economic level and the change of human lifestyle, the prevalence of CCVDs continues to increase. *Ginseng* (*Panax ginseng* C. A. Mey.) was widely used in traditional diseases due to its supposed tonic properties. Ginsenoside Rb_1 (G-Rb_1) is the most abundant active ingredient with multiple pharmacological effects extracted from *ginseng*, which has been shown to have potential benefits on the cardiovascular system through a variety of mechanisms, including anti-oxidation, anti-inflammatory, regulation of vasodilation, reduction of platelet adhesion, influence of calcium ion channels, improvement of lipid distribution, involving in glucose metabolism and controlling blood sugar. This review reviewed the protective effects of G-Rb_1 on CCVDs and its potential mechanisms, such as atherosclerosis (AS), hypertension, coronary heart disease (CHD), ischemic stroke (IS) and periocular microvascular retinopathy. Finally, we reviewed and reported the results of *in vivo* and *in vitro* experiments using G-Rb_1 to improve CCVDs, highlighted its efficacy, safety, and limitations.

Contents

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1. Introduction

For decades, cardiovascular and cerebrovascular diseases (CCVDs) have been the leading cause of death globally. In 2021, 20.5 million people died from CCVDs, the figure that around one-third of all global deaths (Di Cesare et al., 2024). The United Nations has identified non-communicable diseases (NCDS), including CCVDs, as a major global health concern and has set out significant plans to reduce the impact of the disease in all regions (Adeniji & Obembe, 2023; Bonita et al., 2013). At the same time, global awareness of CCVDs prevention has increased. Diet high in sugar and fat has gradually been defined as unhealthy diets, and all kinds of sports are enthusiastically pursued. The induction factors of CCVDs are various, mainly caused by smoking, unhealthy diet, obesity, lack of exercise, alcoholism, hypertension, diabetes and hyperlipidemia, and most CCVDs is preventable. Over the past years, researchers have conducted in-depth studies on the pathogenesis of CCVDs. Atherosclerosis (AS) is the first and key step of all CCVDs. Inflammation and oxidative stress are the main initiators and accelerating mediators respectively in AS, which promote the oxidation of low-density lipoprotein (LDL) in endothelial cells (ECs), induce endothelial dysfunction, and eventually lead to plaque and thrombosis (Hajjar & Gotto, 2013; Pashkow, 2011). *Ginseng Radix* et *Rhizoma* (roots of *Panax ginseng* C. A. Mey.) is a traditional medicine of the Araliaceae family, often referred to as the "king of herbs", and has been used in Eastern countries for thousands of years (Xia et al., 2023). However, the most of the pharmacology and medical research on ginseng has focused on ginsenosides (Kim, 2018). Up to now, nearly 400 ginsenosides have been reported. Ginsenoside-Rb_1 (G-Rb_1) is considered to be one of the main ginsenosides, which has many pharmacological activities due to its steroid structure, such as anti-inflammatory, antioxidant, regulating lipid abnormalities, restoring autophagy (Kim et al., 2018; Kim, 2018). In addition to their therapeutic potential was proven in chronic diseases such as nervous system, cardiovascular system and diabetes, G-Rb_1 has been used in clinical medicine around the world and may provide the basis for the development of novel drugs (He et al., 2018; Mohanan et al., 2018).

Ginsenosides all have a similar basic structure, containing 30 carbon atoms arranged into four rings of steranosteroid nuclei (Zhou et al., 2023). G-Rb_1 belongs to triterpenoids, in addition to G-Rb_2, G-Rg_3 and so on, but G-Rb_1 accounts for a large proportion. The molecular formula of G-Rb_1 is $C_{54}H_2O_{23}$ and its structure is shown in Fig. 1. Many studies have shown that G-Rb_1 can prevent and treat a variety of CCVDs, such as AS, myocardial hypertrophy, arrhythmia, heart failure, and hypertension, by exerting antioxidative stress, anti-inflammatory, anti-apoptotic effects, and regulating calcium channels (Xue et al., 2021). However, up to now, our studies on the pharmacological activity and mechanism of G-Rb_1 against CCVDs have not been systematically summarized. Because of its high safety, G-Rb_1 is expected to be a potential drug for the treatment of CCVDs.

Therefore, this review aims to comprehensively review ameliorative effect of G-Rb_1 on CCVDs through literature search, and systematically expounded the pharmacological action and related mechanisms of G-Rb_1. Especially in atherosclerosis, hypertension, coronary heart disease, ischemic stroke, and periocular microvascular retinopathy.

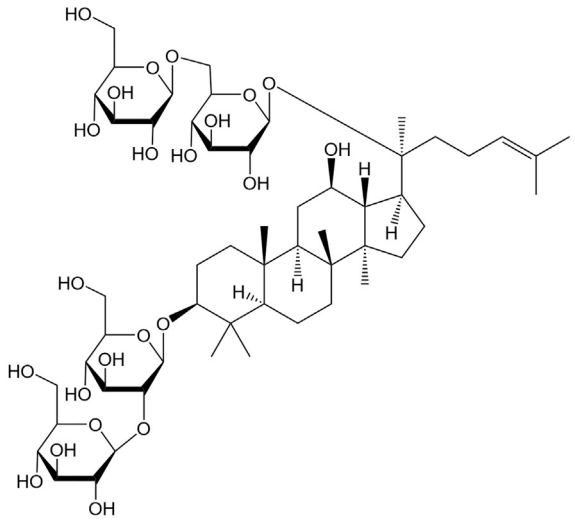

Fig. 1. Chemical structure of G-Rb_1.

2. Atherosclerosis

2.1. Pathogenesis of atherosclerosis

Atherosclerosis (AS) is a chronic inflammatory vascular disease, and its occurrence process involves many complex biological events (Singh et al., 2024). The occurrence of AS usually begins with the injury of arterial ECs (Joshi et al., 2020). ECs are damaged by external factors such as high blood pressure, tobacco, high blood sugar, and oxidative stress, leading to their abnormal function (Sun et al., 2023). Damaged ECs attract and promote the infiltration of LDL into the blood vessel wall. Inside the blood vessel walls, LDL is oxidized to oxidized low-density lipoprotein (ox-LDL), the process that activates an inflammatory response that attracts white blood cells and other inflammatory cells. Ox-LDL forms lipid plaques along with white blood cells and inflammatory cells, which gradually accumulate and expand to form atherosclerotic plaques (Catar et al., 2022). Some plaques may be unstable and prone to rupture due to factors such as internal inflammation and apoptosis. After the plaque ruptured, platelets accumulate on the walls of the damaged blood vessels, prompting the formation of clots (Asada et al., 2020). These clots can partially or completely block blood vessels, leading to serious complications such as myocardial infarction and stroke (Kumar et al., 2024). Overall, AS is a progressive disease involving multiple biological events, including endothelial damage, lipid deposition, plaque formation, plaque rupture, and thrombosis (Libby, 2021). Early intervention and management of the occurrence of AS are of great significance for the prevention of cardiovascular events.

AS is a chronic cardiovascular disease that endangers human health and is one of the most common causes of death. It is known that AS is the pharmacological basis of a variety of cardiovascular diseases. Currently, drug treatment for AS often involves several

types of drugs, including lipid-lowering drugs such as statins, antiplatelet drugs such as aspirin, anti-hypertensive drugs, and antithrombotic drugs (Fan & Watanabe, 2022). At the same time, lifestyle interventions have also significantly influenced the development of AS, including improving dietary habits, reducing the intake of saturated fat and cholesterol, increasing dietary fiber intake, and engaging in moderate exercise (Kirkpatrick et al., 2023). Among them, statins are recognized as the most effective and commonly used treatment, but there are still inevitable risks. Long-term use of statins may lead to muscle pain, abnormal liver function, digestive tract damage, and other adverse effects (Zhao et al., 2023). For this reason, researching and developing natural products that is easily accessible. Natural products to antagonize AS has become an irresistible trend due to having low toxicity, and offering abundant yield.

2.2. Anti-AS effect and mechanism of G-Rb_1

The oxidation of LDL and the formation of foam cells are the basis of AS (Orekhov, 2018). Macrophages and other phagocytes take up ox-LDL accumulated in the membrane to form foam cells, which allows lipid droplets to accumulate in the cytoplasm (Orekhov et al., 2020). Qiao et al. studied the effect of G-Rb_1 on lipid accumulation using primary peritoneal macrophages and an AS model in $APOE^{-/-}$ mice, and concluded by oil red O staining that 20 μmol/L concentration of G-Rb_1 reduced ox-LDL-induced lipid accumulation in macrophage foam cells. The same evidence was obtained *in vivo* experiments that the lipid content in plaque was significantly reduced in the group treated with 50 mg/kg G-Rb_1 (Qiao et al., 2017). AS is a complex chronic inflammatory disease, and the inflammatory response runs through the whole process of AS, so the "inflammation theory" has become a research focus (Liu et al., 2020). Macrophages reflect the inflammatory expression of AS through subtype transformation, which is called "polarization of macrophages" (Moore et al., 2013). Macrophage polarization and inflammatory response regulates the stability of AS plaques (Zheng et al., 2022). One study showed that G-Rb_1 promoted the polarization of M2 macrophages and inhibited the inflammatory response in AS. Specifically, 50 mg/kg G-Rb_1 enhanced the stability of AS plaques in $APOE^{-/-}$ mice by promoting the polarization of M2 macrophages. The mechanism is mainly achieved by increasing the production of interleukin 4 (IL-4) and interleukin 13 (IL-13) and continuous phosphorylation of signal transducer and activator of transcription 6 (STAT6) (Zhang et al., 2018b). Studies have shown that oxidative stress is a key feature of AS (Witztum & Berliner, 1998). Oxidative stress occured when the excess ROS produced exceeds the resistance of the anti-oxidant system (Li et al., 2014). Nuclear factor erythroid 2-related factor 2 (Nrf2) is an endogenous anti-oxidant, when ECs are in an oxidative state, Nrf2 is activated via escaping kelch-like ECH-associated protein 1 (Keap1)-mediated repression and enters into the nucleus, resulting the expression of anti-oxidant proteins such as heme oxygenase 1 (HO-1) (Niture et al., 2014). Wang et al. discovered that G-Rb_1 promoted Keap1 to interact with an E3 ligase SYVN1 at specific lysine residues (K108, K323, and K551) and accelerated its ubiquitination degradation, promoting Nrf2 to release and translocating into the nucleus, thus ameliorating the oxidative stress in ECs induced by high glucose/oxidized low-density lipoprotein (HG/ox-LDL) (Z. C. Wang et al., 2022). It has been reported that the development and stability of AS plaques is closely related to the hyperplasia of vasculature (Khurana et al., 2005; Sedding et al., 2018). Pigment epithelial-derived factor (PEDF) is an endogenous angiogenesis inhibitor that inhibits ECs migration, angiogenesis, and reduces the levels of angiogenesis factors (Dawson et al., 1999; Zhang et al., 2016). Yang et al. established an *in vivo* AS model by feeding $APOE^{-/-}$ mice with HFD, and found that intraderitoneal injection of 50 mg/kg G-Rb_1 could inhibit the proliferation of the vasculium, enhance plaque stability, induce the expression of PEDF, and reduce the production of miR-33. The overexpression of miR-33 confirmed the anti-angiogenic effect of G-Rb_1 through miR-33-mediated PEDF elevation (Yang et al., 2021). Inflammatory mediators (such as IL-1β, TNF-α) play an important roles in all stages of AS, including plaque formation, plaque instability, and plaque rupture (Chan & Ramji, 2022). Studies have shown that G-Rb_1 have significant anti-inflammatory properties and can regulate the inflammatory response through various pathways, thereby positively affecting the development of AS. Firstly, 10 mg/kg G-Rb_1 is taken orally inhibited the release of inflammatory mediators in western diet-fed $APOE^{-/-}$ mice, such as TNF-α and IL-6 (Zhou et al., 2018). Nuclear factor kappa-B (NF-κB p65) was an important transcription factor that regulated the expression of various inflammation-related genes, including adhesion molecules, inflammatory mediators, and cytokines (Liu et al., 2024). In the TNF-α-induced human umbilical vein endothelial cells (HUVECs) injury model, G-Rb_1 preconditioning inhibited intracellular oxidative stress levels and inflammatory responses, and its protective effect was related to the NF-κB p65 pathway. Importantly, the addition of the anisomycin (p38 and JNK activator) demonstrated that G-Rb_1 exerted cytoprotective effects through the p38 and JNK-mediated NF-κB p65 pathway (Zhou et al., 2017). Vascular smooth muscle cells (VSMCs) contributed to structural changes in the artery wall, such as the proliferation of subintimal connective tissue and deposition of collagen (Finney & Orr, 2018). Lu et al. confirmed the protective effect of 20 μmol/L G-Rb_1 on Human Coronary Artery Smooth Muscle Cells (HCASMC) and elucidated the mechanisms associated with reducing ROS production and increasing superoxide dismutase (SOD) activity (Lu et al., 2023b). Autophagy is a crucial cellular self-repair mechanism that maintains homeostasis (Gubas & Dikic, 2022). Moreover, autophagy is intricately linked to lipid metabolism (Xie et al., 2020). Autophagy is implicated in regulating the degradation process of liposomes and mitochondria, thereby influencing cholesterol metabolism and the lipid channels of ECs, ultimately impacting the progression of AS (Plakkal Ayyappan et al., 2016). The B-cell lymphoma-2 (Bcl-2) proteins antagonizes apoptosis via a combination of Bcl-2-associated X (BAX) protein with heterodimer formation, it also regulates autophagy by regulating BECN1/beclin-1 (Liu et al., 2018b). G-Rb_1 has been shown to have a protective effect on mitochondrial apoptosis by regulating Bcl-2 family proteins (Wang et al., 2018). Zhou et al. found that after eight weeks of 10 mg/kg G-Rb_1 administration in $APOE^{-/-}$ mice, lipid levels were significantly reduced, plaque area was reduced, Bcl-2 expression was increased, cleaved-caspase-3, 9/caspase-3, 9 expression was weakened. The mechanism is LC3 was transformed from type I to type II, and autophagy flux was increased to inhibit apoptosis (Zhou et al., 2018). Simultaneously, G-Rb_1 reduced lipid accumulation in macrophage foam cells and enhanced the stability of arteriosclerotic plaques by inducing macrophage autophagy, providing new evidences for the possible mechanism of G-Rb_1 in the prevention and treatment of AS (Qiao et al., 2017). A study suggested that selective removal of senescent ECs may be a new strategy for the prevention and treatment of AS (Cho et al., 2020). The study demonstrated that G-Rb_1 alleviated ox-LDL-induced HUVECs aging and restored the reduction of silent information regulator 1 (SIRT1) and autophagy, which was related to its anti-aging effect (Shi et al., 2020a). G protein-coupled estrogen receptor (GPER) is a transmembrane receptor implicated in rapid estrogen signaling. Estrogen regulates a variety of cell signaling pathways by acting on GPER, influencing biological processes and playing an important role in combating the occurrence and development of AS (Meyer et al., 2014). In a rabbit model of AS, 20 mg/kg G-Rb_1 promoted the survival and repair of vascular ECs. It promoted the repair and regeneration of damaged cells by activating the PI3K/Akt pathway

and enhanced the function of ECs, thereby alleviating the pathological process of AS. Studies have proved that the PI3K/Akt pathway signaling pathway was regulated by GPER (Yang et al., 2019). The imbalance of intestinal flora may have promoted the process of AS by affecting metabolic abnormalities, exacerbating chronic inflammation, and affecting immune system function (Jonsson &Bäckhed,2017). It's worth noting that G-Rb_1 could effectively relieve AS symptoms by restoring intestinal flora. 20 mg/kg G-Rb_1 oral therapy altered intestinal microbial composition and short-chain fatty acid concentrations and depletion of desulphurizing bacteria, accompanied by increasing production of acetic acid and propionic acid. In addition, non-targeted metabolomics showed that G-Rb_1 significantly improved the fecal metabolite profile, especially arachidonic acid metabolism and primary bile acid biosynthesis (Liang et al., 2024). The emergence of new drug formulations, including nanoparticles coated with biomimetic cell membranes, improved the problem of drug targeting. Yin et al. prepared Se/G-Rb_1-NPs by wrapping Se and G-Rb_1 in platelet membrane. The nanoparticles coated in platelet membrane retain the inherent elements of platelets, deliver drugs to plaques, and maximize the anti-AS effect of G-Rb_1 (Yin et al., 2022). High cholesterol increases the risk of AS. A study verified the protective effect of G-Rb_1 on hypercholesterol-induced damage of human hepatocellular carcinomas (HepG2) cells to improve AS by reducing intracellular cholesterol levels and inhibiting the expression of membrane transporters ATP-binding cassette transporter A1 (ABCA1) and ATP binding cassette subfamily G member 1 (ABCG1) by regulating the SREBP-2-HMGCR and LXR-IDOL signaling pathways (Cecarini et al., 2023). Studies have shown that G-Rb_1 has a significant pharmacological effect against AS, and the literature collected from multiple databases is shown in Table 1.

3. Hypertension

3.1. Pathogenesis of hypertension

Hypertension is a common chronic disease that is more common in the elderly. However, in recent years, with the change of lifestyle and diet structure, hypertension patients have shown a trend of "younger" (Samuels et al., 2019). Hypertension is also one of the important causes of premature death in the world. Prevention and treatment of hypertension is of great significance to reduce the incidence and mortality of CCVDs (Kahan, 2019). It is well known that high blood pressure is associated with a greater incidence of cardiovascular disease than normal blood pressure. This indicated the greater liability of hypertensives to die of causes related to the cardiovascular system (Doyle, 1991). The pathogenesis of hypertension is still unclear, although genetic factors and environmental factors play an important role, but recent studies have found that the influence of personal lifestyle has become a key factor inducing the occurrence and development of hypertension (Tylicki & Rutkowski, 2003). The modern treatment of hypertension is mainly based on drugs to lower the patient's blood pressure and protect the target organs (Guerrero-García & Rubio-Guerra, 2018; Laragh, 1988). Representative drugs include calcium channel blockers-felodipine, angiotensin-converting enzyme inhibitors (ACEI)-perindopril, angiotensin-II receptor blockers-irbesartan, β-blockers-bisoprolol, and diuretics-hydrochlorothiazid (Mann, 2011; Omboni & Volpe, 2018). While these drugs can lower a patient's blood pressure, they do not prevent hypertension. However, researches showed that finding medicines from traditional Chinese herbs to treat and prevent hypertension is a very important and effective means (Nyulas et al., 2024). Ginseng is an ancient perennial herb, and studies have shown that its chemical composition has great potential for the treatment and prevention of hypertension (Karmazyn & Gan, 2021).

3.2. Anti-hypertension effect and mechanism of G-Rb_1

Nitric oxide (NO) is considered to be an important pathway involved in the regulation of hypertension and vascular tone (Kublickiene et al., 1997). It is known that ECs generate NO from *L*-arginine via the catalytic action of eNOS (Closs et al., 2004). Inhibition of eNOS activity is known to affect the release of NO in the blood vessel wall. Studies have shown that G-Rb_1 significantly reduced tail blood pressure in spontaneously hypertensive rats (SHR), and revealed its endothelium-dependent vasodilation through activation of the PI3K/Akt pathway followed by phosphorylation of eNOS and production of NO. Further studies have reported that G-Rb_1 activated cationic amino acid transporter-1 (CAT-1) to stimulate *L*-arginine transport and uptake into ECs, thereby enhancing eNOS catalysis to produce more NO (Pan et al., 2012a). Furthermore, endothelial dysfunction and senescence is closely related to hypertension. G-Rb_1 improved H_2O_2-induced senescence and dysfunction of HUVECs by regulating SIRT1/AMPK signaling pathway, and the related mechanism is related to the up-regulation of eNOS expression and NO production (Zheng et al., 2020). Pulmonary arterial hypertension (PAH) is a common form of high blood pressure characterized by increased tension in the blood vessels of the lungs, eventually leading to right heart failure and death (Huetsch et al., 2016). One study showed that G-Rb_1 improved pulmonary hemodynamic parameters, pulmonary artery wall thickening, and right ventricular hypertrophy in PAH rats, providing evidence of a preventive effect on PAH by inhibiting store-operated calcium entry (SOCE) complexes and associated calcium entry (Wang et al., 2020b). In the cyclopiazonic acid (CPA)-induced pulmonary artery smooth muscle cell (PASMCs) model, G-Rb_1 attenuated CPA induced PA contraction, Ca^{2+} inflowing, and Mn^{2+} quenching, and the vascular relaxation effect of G-Rb_1 is completely eliminated under the action of SOCE blockers. These results all showed the attenuation of G-Rb_1 to SOCE (Wang et al., 2015). Hypertension is a well-known risk factor for intracranial aneurysm (IA). IA is a condition in which the artery wall expands or bulges locally, potentially leading to rupture and bleeding. high blood pressure increases the risk of IA by putting excessive pressure on the artery wall (Shang et al., 2023).The gut microbiome is symbiotic with the human body and has a significant impact on human health (Jia et al., 2022). A recent analysis of intestinal flora and metabolome in IA rats with hypertension showed that G-Rb_1 treatment increased the abundance of intestinal flora and improved the balance of intestinal flora. Importantly, the study also found that several gut metabolites of G-Rb_1, such as prostaglandins F2a and vitamin D2, all played a role in regulating blood pressure (Zeng et al., 2023). One of the main mechanisms of hypertension in SHR is the activation of the congenital anomaly renin angiotensin system (RAS) (Williams et al., 1982). Angiotensin II (Ang II) is a key factor in RAS, which increased blood pressure and induced inflammation, endothelial damage, and fibrosis in various organs (Duprez, 2006). The results showed that RAS activity was weakened in the myocardium of G-Rb_1, and angiotensin-converting enzyme 2 (ACE2, an enzyme that degrades AngII) was activated by G-Rb_1 to degrade AngII, but RAS activity remained high in serum. The mechanism of this action is still unknown (Jiang et al., 2017). Hypertension and its complications are related to arterial remodeling. Transient receptor potential cation channels (TRPC) is an important non-selective cation channels that regulate calcium homeostasis in mammalian cell membranes. With the increase of age and tail artery systolic blood pressure, carotid artery remodeling in SHR rats gradually increased, and the expression of TRPC1, 6 increased significantly. Importantly, after G-Rb_1

Table 1
Study on G-Rb_1 anti-AS model, action and mechanisms.

Type	Inducer	Animal/Cell	Dose	*In vivo* delivery mode	Effects	Mechanisms	References
In vivo; *In vitro*	HFD; ox-LDL	$APOE^{-/-}$ mice; Peritoneal macrophages	50 mg/kg; 20 μmol/L	i.p	Lipid accumulation in macrophage foam cells↓; Autophagy flux in macrophage foam cells↓	AMPK; LC3II; SQSTM1/p62	Qiao et al., 2017
In vivo; *In vitro*	HFD; LPS	$APOE^{-/-}$ mice; Peritoneal macrophages	50 mg/kg; 20 μmol/L	i.p	Plaque stability↑; Inflammatory reaction↓	STAT6 phosphorylation; M2 macrophage polarization	Zhang et al., 2018b
In vivo; *In vitro*	STZ + HFD; D-GLU and ox-LDL	$APOE^{-/-}$ mice; EAhy926	50 mg/kg; 10 μmol/L	i.p	Oxidative stress↓; Apoptosis and inflammation↓; Degree of atherosclerosis in mice↓	Nrf2 and Keap1 dissociation; Nrf2 nuclear translocation; Nrf2/PGC-1α complex formation	Wang et al., 2022b
In vivo	HFD	$APOE^{-/-}$ mice;	50 mg/kg	i.p	Extravascular hyperplasia↓; Inflammatory reaction↓; Plaque stability↑	PEDF; miR-33	Yang et al., 2021
In vitro	Resistin	HCASMC and VSMCs	20 μmol/L		HCASMC proliferation ↑; HCASMC migration↓; ROS level↓; Mitochondrial SOD activity↓	ROS; SOD	Lu et al., 2023b
In vivo	Western diet	$APOE^{-/-}$ mice	10 mg/kg	i.g	Serum lipid levels↓; Inflammatory factors in serum↓; Apoptosis levels in the aorta ↓; Autophagy levels ↓	BCL-2/BAX/caspase-3/caspase-9; LC3I/II	Zhou et al., 2018
In vitro	TNF-α	HUVECs	20 μg/mL		Cell viability↑; Cellular inflammation level↓; Cellular oxidative stress levels↓; Apoptosis↓ Mitochondrial membrane potential↑; NF-κB nuclear transcription↓	JNK/p38 /NF-κB	Zhou et al., 2017
In vivo; *In vitro*	HFD; ox-LDL	SD rats; HUVECs	40 mg/kg; 80 μmol/L	i.p	Endothelial senescencel↓; Autophagy↑; Myocardial senescence↓	SIRT1/Beclin-1/autophagy axis	Shi et al., 2020a
In vivo; *In vitro*	HFD with balloon catheter injury	New Zealand rabbits; Endothelial cells isolated from rabbits	20 mg/kg; 80 μmol/L	i.g	Levels of blood lipids↓; Apoptosis and inflammatory response in ECs↓	GPER-mediated PI3K/Akt pathway	Yang et al., 2019
In vivo	HFD; Vitamin D3	Sprague-Dawley rats	20 mg/kg	i.g	Plaque buildup and inflammatory infiltration↓; dyslipidemia↓↓; Liver cell swelling and inflammation↓; F/B ratio of intestinal flora↓; Generation of SCFAs↑;	Gut microbiome/Short-chain fatty acids/arachidonic acid metabolism/primary bile acid synthesis	Liang et al., 2024
In vitro	HFD; ox-LDL	HepG2 cells	50 μmol/L		cholesterol levels↓	SREBP-2-HMGCR and LXR-IDOL	Cecarini et al., 2023

treatment, TRPC1, 6 expression was significantly inhibited, tail artery systolic blood pressure decreased, and carotid artery remodeling was relieved (Lin et al., 2015). Tengdan Capsule (TDC) is a capsule made of a pure herbal compound that is used in hospitals and pharmacies in China to treat mild and moderate hypertension. Seven compounds, including G-Rb_1, were identified from the water-soluble extracts of TDC by HPLC. The kidney is a vital organs for excreting waste and maintaining water balance, electrolytes, acids and alkalis. It plays a role in the maintenance of normal blood pressure. Hypertension is also an important risk factor for the progressive decline of renal function in patients with nephropathy (Griffin, 2017). Studies have shown that TDC effectively reduced blood pressure in SHR rats and prevented kidney damage caused by SHR hypertension. From a mechanism perspective, TDC blocked periosteal protein-mediated inflammatory response by regulating TGF-β/Smad signaling pathways in the kidney, and *in vitro* studie has also shown that TDC down-regulated periosteal protein expression in human embryonic kidney cell 293 (HEK293) injury models. Therefore, prevention of periosteal protein-mediated renal fibrosis and inflammation may be a promising strategy for the treatment of hypertensive renal injury (Du et al., 2021). The literatures on G-Rb_1 resistance to hypertension collected from multiple databases is shown in Table 2.

4. Coronary heart disease

4.1. Pathogenesis of coronary heart disease

Coronary heart disease (CHD) is a chronic disease that begins in childhood, even if symptoms first appear in middle age (Jokinen, 2015). CHD is caused by the gradual narrowing of the coronary arteries due to plaque buildup or atherosclerosis. Eventually, severe obstruction of the vascular lumen can lead to myocardial ischemia, hypoxia, and cardiomyocyte necrosis. CHD is characterized by heart failure, arrhythmia, and severe sudden death (Lu et al., 2022). Angina pectoris is one of the early symptoms of CHD (Oram et al., 1972), patients will have discomfort or pain in the precardiac area of the chest, prone to arrhythmia symptoms. Severe cases of arrhythmia can lead to cardiac arrest (Lin et al., 2018). Therefore, angina pectoris, myocardial infarction, arrhythmia, sudden death and other cardiovascular diseases are a serious of life-threatening disease for patients. It is very important to prevent the occurrence of CHD. There are several types of drugs that can be used for the clinical treatment of CHD, including statins, aspirin, anti-platelet drugs, and calcium channel blockers. Due to strong progress in clinical studies, the pathophysiology of CHD and the mechanisms of action of drugs used to treat CHD is constantly being updated, with the discovery of new drugs including proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and sodium-glucose co-transporter 2 (SGLT2) inhibitors (Sabouret et al., 2022). *Ginseng* is a traditional Chinese herb that has been used for centuries in food preparation and traditional medicine, its clinical safety is higher than that of several chemical synthetic drugs. There have been numerously reported about *ginseng* and its extracts in the prevention and treatment of CHD (Aminifard et al., 2021). Therefore, *ginseng* and its extracts are promising candidates for the treatment of CHD. Here, we summarize the effects and mechanisms of G-Rb_1 in alleviating CHD, providing references for the clinical development and application of *ginseng* as an alternative therapy for CHD.

4.2. Anti-CHD effect and mechanism of G-Rb_1

Many factors contribute to CHD and subsequent cardiovascular events. Among them, obesity has become a major health problem with social and economic implications (Calabro & Yeh, 2008). Resistin, a newly described adipokine, is thought to play a role in the development of insulin resistance and obesity, contributing to the development of tubular arteriosclerosis and CHD (Lazar, 2007). The multifaceted properties of G-Rb_1 make it becomes a promising candidate for the prevention and treatment of vascular disease. In a human recombinant resistin induced human coronary endothelial cell (HCAEC) model, G-Rb_1 blocked resistin due to inducing downregulation of eNOS protein and inhibiting intracellular excess ROS production (Chen et al., 2010). In ECs, eNOS is considered to be the most important factor in maintaining normal blood vessel function (Kawashima & Yokoyama, 2004). ROS has been shown to be a key mediator in the formation of vascular inflammation (Madamanchi et al., 2005). Therefore, we conclude

Table 2
Study on G-Rb_1 anti-hypertension model, action and mechanisms.

Type	Inducer	Animal/Cell	Dose	*In vivo* delivery mode	Effects	Mechanisms	References
In vivo; *In vitro*	SHR; Glutamine and antibiotics	SHR; PAEC	100 mg/kg; 10 μmol/L	i.v	SHR blood pressure↓; Rat blood vessels dilated↑; NO production↑	PI3K/Akt/eNOS pathway; L-arginine transport; NO	Pan et al., 2012b
In vitro	H_2O_2	HUVECs	20 μmol/L		Cell aging↓; Cellular oxidation and inflammation↓	SIRT1/AMPK/PAI-1/ eNOS/NO	Zheng et al., 2020
In vivo	MCT	Sprague-Dawley rats	30 mg/kg;	i.p	Hemodynamic force↓; Pulmonary vascular remodeling↓; Right ventricular systolic pressure↓	STIM1/TRPC1 /TRPC4/ SOCE	Wang et al., 2020a
In vivo; *In vitro*	CH/MCT; ET-1	Sprague-Dawley rats; PASMC	50 mg/kg 10 μmol/L	i.p	Vascular relaxation↑; PA contraction↓; Ca^{2+}↓	SOCE/Ca^{2+}	Wang et al., 2015
In vivo	SHR	SHR	60 mg/kg	i.p	Rat blood pressure↓; Intestinal tract microbial population↑;	Regulate intestinal flora	Zeng et al., 2023
In vivo	SHR	SHR	50 mg/kg	i.p	Cardiac function injury↓; Heart weight index↓; Myocardial inflammatory factor↓	Cardiac function recovery; Ventricular remodeling; RAS	Park et al., 2023

that G-Rb_1 has potential clinical applications in blocking resistin induced endothelial dysfunction, and thus becomes a candidate for the prevention of CHD. Heart failure (HF) is a clinical syndrome caused by the development of various heart diseases to a certain serious stage, and CHD can lead to HF. One study showed that G-Rb_1 reduced heart rate, improved cardiac function, and mitigated HF-induced histological changes in HF rats, and molecular mechanism studies suggest that G-Rb_1 alleviated HF by restoring heart/mitochondrial function, increasing glucose uptake, and preventing cardiac remodeling through TGF-β1/Smad, ERK, and Akt signaling pathways (Zheng et al., 2017a). Mitochondria are the powerhouse of cells and play an integral role in many heart diseases, including HF. HF and poor cardiac remodeling are often accompanied by increased glycolysis and decreased fatty acid oxidation (FAO) (Rosenblatt-Velin et al., 2001). Proliferator-activated receptor-alpha (PPARα) activation to regulate energy metabolism plays a critical role in the treatment of cardiac diseases (Bougarne et al., 2018). It's also reported that the activation of PPARα in the progressive phase of HF could maintain myocardial function and energetics by increasing FAO and ATP supply (Kaimoto et al., 2017). The fas associated death domain (FADD) is involved in cellular glycolipid metabolism and inflammatory processes (Mouasni & Tourneur, 2018). In isoproterenol (ISO)-induced HF rats and neonatal rat cardiomyocyte (NRCM) models, studies have shown that G-Rb_1 alleviated HF cardiac energy disturbance and adverse pathological remodeling by promoting FAO and ATP synthesis and improving mitochondrial function. It is also demonstrated that G-Rb_1 played a cardioprotective role by regulating the FADD/PPARα axis (Li et al., 2023). In addition, functional adenosine 5′-monopho sphate-activated protein kinase (AMPK) is known to help restore the efficiency of myocardial contraction, which is one of the basic conditions for maintaining heart function (Juric et al., 2007). Studies have shown that G-Rb_1 regulated cardiometabolic remodeling by improving FAO in failing hearts. In addition, the effect of G-Rb1 can be mediated by activation of AMPK (Kong et al., 2018). It has been reported that G-Rb_1 inhibits cardiomyocyte autophagy by regulating Rho/ROCK and PI3K/mTOR pathways, and played a role in resistance to HF (Yang et al., 2018). Cardiomyocyte apoptosis is a potential mechanism of heart disease and lead to HF (Geng et al., 1999). It has been known that stimulation of the beta-adrenergic agonists causes hypertrophy and apoptosis in cardiomyocytes (Krishnamurthy et al., 2007). Studies have shown that G-Rb_1 reduced isoproterenol (ISO)-induced apoptosis of rat cardiomyocytes (H9c2) and decreased the expression of caspase-3 and caspase-9 (Wang et al., 2013). Cardiac hypertrophy is an independent risk factor for adverse clinical outcomes in patients with cardiovascular disease. Persistent cardiac hypertrophy may progress to HF (Vakili et al., 2001). Inflammation has been proposed as a drug target for the treatment of heart hypertrophy and HF. Effective mechanism-based interventions at the stage of heart hypertrophy can delay or mitigate the deterioration of heart morphology and function. In cardiomyocytes, G-Rb_1 prevented myocardial hypertrophy by maintaining mitochondrial function, and in macrophages, G-Rb_1 partially reduced the inflammatory response of activated macrophages by inhibiting MAPK signaling and MEK1/2 activation. In addition, miR-155 partially participates in G-Rb_1′s inhibition of IL-6 production in activated macrophages. It is suggested that G-Rb_1 regulated the crosstalk between activated macrophages and cardiomyocytes in patients with cardiac hypertrophy (Wang et al., 2021a). Given the great therapeutic potential of G-Rb_1 for HF, the researchers increased its effectiveness by formulating it into nanoparticles. Therefore, GRb1@PLGA@NPs was prepared and an *in vitro* oxidative stress model was established using H9c2 cardiomyocytes, and an *in vivo* HF model was established in SD rats. *In vitro* experiments have shown that G-Rb_1 nanomaterials can effectively regulate the oxidative damage of cardiocytes induced by hypoxia and reoxygenation, and *in vivo* experiments have further shown that G-Rb_1 nanomaterials reduced the level of inflammation in heart tissue and the mechanism of HF treatment is related to the regulation of organism energy metabolism through ROS/PPARα/PGC1α pathway (Du et al., 2023). The literatures on G-Rb_1 resistance to CHD collected from multiple databases is shown in Table 3.

5. Ischemic stroke

5.1. Pathogenesis of ischemic stroke

Ischemic stroke (IS) is the sudden rupture or ischemia of the cerebral blood vessel caused by cerebral artery thrombosis or embolism, resulting in insufficient blood supply to specific parts of the brain, especially the middle cerebral artery, resulting in insufficient supply of nutrients, oxygen and glucose, energy imbalance, and ultimately lead to the death of neurons (Dong et al., 2022). IS is a pathological condition characterized by vascular occlusion and insufficient blood supply (Kalogeris et al., 2016). Thrombolytic therapy aims to restore cerebral perfusion in time and is the main treatment strategy for IS (Stoll et al., 2008). However, reperfusion may promote secondary cell death and exacerbate brain damage, leading to cerebral ischemia/reperfusion injury (CIRI) (Datta et al., 2020).The occurrence and development of IS include neuronal excitatory toxicity, mitochondrial dysfunction, neuroinflammatory injury, oxidative stress and so on (Guo et al., 2009). Therefore, the occurrence and development of IS are complex, making it very difficult to treat. Tissue plasminogen activator (T-PA) is the only ischemic stroke treatment approved by the U.S. Food and Drug Administration (FDA). However, T-PA has a limited time window of 6 h, and delayed infusion of T-PA increases the risk of bleeding conversion and leading to high mortality (Hacke et al., 2008). Natural products played an important role in ancient traditional medical systems and are still widely used today. In recent years, it has been reported that a large number of natural products have proved beneficial to stroke worldwide, and the therapeutic effect of ginseng and its natural products has attracted the attention of researchers in particular (Fei et al., 2020). Through systematic analysis, it was found that G-Rb_1 has a potential neuroprotective effect, mainly by weakening the brain water content, promoting neurogenesis, anti-apoptosis, anti-oxidant, anti-inflammatory, energy supplement and brain circulation bioactivity in the treatment of IS (Shi et al., 2020b).

5.2. Anti-IS effect and mechanism of G-Rb_1

The brain requires neurons to maintain high levels of mitochondrial oxidation to meet its energy requirements for normal functioning. Neuroprotection is a reliable treatment for IS (Patel & McMullen, 2017). In IS, the oxygen supply to the mitochondria is impaired, resulting in excess ROS production in neurons, which is an initial cause of IS in brain (Chouchani et al., 2014). Astrocytes are the most abundant cells in the brain, which support the survival and function of neurons from different physiological perspectives (Ioannou et al., 2019). Firstly, Ni et al. used the intracerebral CD38 (Cluster of differentiation 38) knockout method combined with photochemotherapy to construct cerebral thrombosis model *in vivo*. Intra-abdominal injection of 100 mg/kg G-Rb_1 for five consecutive days inhibitted intracerebral ROS production, reduced lactate dehydrogenase (LDH) release, and alleviated oxidative damage and glutamate accumulation. Secondly, they cultured primary astrocytes in a sugar-free medium with hypoxia for 4 h, then supplemented with glucose and oxygenated for 1 h to simulate ischemia and reperfusion injury during IS. It was found that 20 μmol/L

Table 3
Study on G-Rb_1 anti- CHD model, action and mechanisms.

Type	Inducer	Animal/Cell	Dose	*In vivo* delivery mode	Effects	Mechanisms	References
In vitro	Resistin	HCAEC	20 μmol/L		eNOS expression and NO level↑; ROS generation↓; Oxidative stress level↓	p38/JNK/eNOS/NO	Chen et al., 2010
In vivo	Coarctation of abdominal aorta	Sprague-Dawley rats	70 mg/kg; 40 μmol/L	i.p	Hemodynamic force↓; Myocardial fibrosis↓; Cardiomegaly↓; Mitochondrial membrane potential↑	GLUT4/TGF-β1/Smad/ERK/Akt	Zheng et al., 2017b
In vivo; In vitro	ISO; ISO	Sprague-Dawley rats; NRCM	80 mg/kg; 10 μmol/L	i.g	Cardiac function↑; Left ventricular volume↑; Cardiac hypertrophy and fibrosis↓; Cardiac energy metabolism↑	FADD/PPARα	Li et al., 2023; Yang et al., 2019
In vivo	Adr	Wistar rats	60 mg/kg	i.p	Cardiac function↓; Phosphate substrate levels↑; *L*-Carnitine homeostasis imbalance↓	AMPK; Fatty acid beta oxidation	Zhang et al., 2021
In vivo	Overload heart failure	Wistar rats	5 mg/kg	i.p	Myocardial apoptosis↓; Cardiomyocyte autophagy↓	Rho/ROCK; PI3K/mTOR	Cecarini et al., 2023
In vivo; In vitro	ISO; ISO	Sprague-Dawley rats; H9c2	20 mg/kg; 100 μmol/L	i.p	Cell death↓; Apoptosis↓	PKA; caspase-3/caspase-9	Wang et al., 2013
In vivo; In vitro	Ang II; Ang II;	C57BL/6J mice; H9c2	100 mg/kg; 100 μmol/L	i.p	Cardiomegaly↓; Myocardial fibrosis↓; Myocardial ultrastructural injury↓; Cardioinflammation↓	MAPK/MEK1/2; miR-155/IL-6	Wang et al., 2021a

G-Rb_1 pretreatment reduced intracellular calcium overload, prevented activation of astrocytes and blocked RET (Succinate driven reverse electron transport)-driven ROS production in mitochondria. (Ni et al., 2022). RET is a major source of ROS (Komlódi et al., 2018). Oxidative stress caused by the imbalance between ROS and the anti-oxidant defense system plays a crucial role in the occurrence and development of IS (Tziveleka et al., 2021). Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) and mitochondrial metabolism are the main sources of ROS (Canugovi et al., 2019) NOX4 is a member of the NOX family and was first discovered in the kidneys (Begum et al., 2022). It is worth noting that NOX4 is highly expressed in brain vessels and is significantly associated with IS, especially increased levels of oxidative stress (Radermacher et al., 2013). G-Rb_1, as a known drug targeting NOX4, has shown efficacy in the treatment of IS (Li et al., 2022). Stroke can cause multiple organ or systemic disease and trigger a systemic response (Santos Samary et al., 2016). Lung infection and stress ulcers are the most common complications in patients with severe IS (Chen et al., 2011). In addition, intestinal permeability was increased and intestinal flora was unbalanced in rats after IS, which was related to the severity of stroke (Crapser et al., 2016). Su et al. established a model of middle cerebral artery occlusion/reperfusion (MCAO/R) *in vivo* to investigate whether G-Rb_1 can ameliorate MCAO/R-induced brain, lung and intestinal injury. The results showed that G-Rb_1 ameliorated brain, lung, and intestinal tissue damage in MCAO/R mice, and identified its underlying molecular mechanisms related to activation of PPARγ (Peroxisome proliferator activated receptor gamma Gene-γ) and inhibition of NF-κB p65 phosphorylation (Su et al., 2022). Brain microvascular endothelial cell (BMEC) is an important part of the neurovascular unit, which can promote angiogenesis and synaptic formation in IS mice after brain parenchymal transplantation (Du et al., 2024). Specifically, Luo et al. used a network pharmacological hybrid computational and experimental study to find that G-Rb_1 regulated the interaction between oxidative stress, apoptosis, and autophagy in BMEC. Key targets such as chelate 1 (SQSTM1/p62), autophagy associated 5 (ATG5) and hypoxia-inducing factor 1-α (HIF-1α) were screened, highlighting their protective role in mediating G-Rb_1 against IS-induced BMEC damage and their molecular mechanisms (Luo et al., 2024). The blood–brain barrier (BBB) is a biochemical barrier that precisely regulates the environmental homeostasis of brain tissue through its ion channels and transporters. When IS occurs, the BBB is disrupted, leading to a range of injuries that aggravate the effects of the disease (Gao et al., 2023). Zona Occludens 1 (ZO-1) anchors other membrane proteins, such as claudin-5, to the cytoskeleton through peripherally associated membrane protein interactions, establishing the integrity of interendothelial connections (Branca et al., 2019). Shengmai San (SMS) is a famous traditional Chinese medicine (TCM) prescription composed of *ginseng*, ophiopogon and schisandra. It has the effect of beneficial *qi* and promoting fluid production. It is often used to treat chronic cough caused by bronchitis and neurasthenia (Ahmed et al., 2020). SMS with G-Rb_1 as the main ingredient has been shown to have a protective effect on BBB dysfunction induced by IS. It also promoted the expression of ZO-1 and claudin-5, increased the expression of tight junction, and inhibited the expression of matrix metalloproteinase 2, 9 (MMP-2, 9) and the phosphorylation of myosin light chain (MLC) (Zhang et al., 2020). IS always occurs in the abnormal microenvironment of the brain, and the formation of the abnormal microenvironment promotes the secondary damage of neurons (Aarts et al., 2002). The overload and increase of intracellular Ca^{2+} and glutamate is a key factor constituting the abnormal microenvironment (Choi & Rothman, 1990). Glutamate transporter-1 (GLT-1) can actively transfer extracellular Glu and maintain a low concentration of extracellular Glu, so it plays an important role in neural activity and protection of neurons

(Rao et al., 2001). Abnormal Ca^{2+} leads to decrease cerebral blood flow in the microenvironment. An abnormal increase in Glu leads to overactivation of the NMDA receptor (NMDAR) and leads to influx of Ca^{2+}, resulting in intracellular Ca^{2+} overload and a range of enzyme activity associated with cytotoxicity (Bano & Nicotera, 2007). Abnormal Glu in the Ca^{2+} microenvironment promotes the release of mitochondrial Cytochrome complex (Cyt-C) and activates the caspase cascade that causes mitochondrial stress and directly regulates apoptosis (Zhao et al., 2010). Wang et al. used microperfusion and photochemical methods to induce thrombosis in cerebral IS rats, and found that intrabitoneal injection of 100 mg/kg G-Rb_1 increased the blood flow in hippocampus of rats, changed the microenvironment in hippocampus, and thus improved the ultrastructure of neurons. The molecular mechanism is that G-Rb_1 up-regulated GLT-1 expression and dose-dependent decreased the expression of NMDAR and Cyt-C (Wang et al., 2017). Cerebral microvascular cell apoptosis is a key factor in IS. G-Rb_1 reduced apoptosis, increased Bcl-2/Bax protein levels, reduced cleaved caspase-3/caspase-3 and p53 levels, and increased angiopoietin-1 (Ang-1) and vascular endothelial growth factor levels (VEGF), promoting the release of angiogenesis regulatory factors (Li et al., 2010; Zhang et al., 2022). Signal transducer and activator of transcription 5 (STAT5) responsive elements in the Bcl-xL promoter become active when treated with G-Rb_1 (Zhang et al., 2006). Subarachnoid hemorrhage (SAH) is a subtype of stroke that accounts for 7% of all strokes each year and has one of the highest mortality and morbidity rates (Chen et al., 2021b). Tang et al. prepared G-Rb_1 carbon quantum dots (RBCQDs), which were distributed in the subarachnoid space by intratheral injection. The results showed that compared with G-Rb_1, RBCQDs not only had better water solubility and anti-oxidant ability, but also had significant iron chelation ability, thus enhancing its effect of alleviating secondary injury after cerebral hemorrhage (Tang et al., 2024). Administration of G-Rb_1 prior to transient IS is known to prevent neuronal death in rats, protect the cerebral cortex from ischemic damage, and provide a protective effect during cerebral ischemia by scavenging excess free radicals (Zhang et al., 1998). IS leads to rapid and severe neurological impairment due to braindamage. Axon regeneration and reconnection play a key role in neural remodeling, which compensates for damaged nerves by rewiring neural networks. Studies have shown that G-Rb_1 improved functional recovery after IS by stimulating axonal regeneration and brain repair. The underlying mechanism may be up-regulation of cAMP/PKA/CREB pathway expression (Gao et al., 2020). The cAMP/PKA/CREB signaling pathway has been shown to be important for axon regeneration (Gao et al., 2004). Gap junctions (GJ) are unique clusters of membrane channels that allow the exchange of small molecules and ions between adjacent cells (Belousov et al., 2017). Connexin (Cx) is the basic structure of GJ. Connexin 43 (Cx43) is widely present in astrocytes and vascular ECs of the central nervous system (Chang et al., 2000). After IS and reperfusion injury, Cx43 mediated the transfer of apoptosis information from the ischemic central region to the adjacent ischemic penumbra through astrocyte GJ, resulting in neuronal cell death and further increase in infarction size (Le et al., 2014). Aquaporin 4 (AQP4) plays an important role in the formation and dissipation of cerebral edema in early IS (Yao et al., 2015). IS involves complex pathological processes and requires multi-target intervention. Drug pairs are the simplest mutually reinforcing form of multi-drug therapy, ginseng and rhubarb are commonly used for IS (Lu et al., 2014). Li et al. established a focal brain I/R model *in vivo* using modified Longa suture method, and found that the combined treatment of G-Rb_1 and emodin could reduce the BBB permeability and cerebral infarction size, the mechanism of which was related to the down-regulated expression of Cx43 and AQP4. Importantly, the combination of G-Rb_1 and emodin was more effective than G-Rb_1 alone (Li et al., 2018). The literatures on G-Rb_1 resistance to IS collected from multiple databases is shown in Table 4.

6. Retinopathy

6.1. Pathogenesis of retinopathy

Retinal disease is a group of high-risk eye diseases, which is the main cause of vision loss and blindness, and the vascular system is the main cause (Li et al., 2021). Regulation of the retinal microenvironment is primarily dependent on the blood-retinal barrier

Table 4
Study on G-Rb_1 anti-IS model, action and mechanisms.

Type	Inducer	Animal/Cell	Dose	*In vivo* delivery mode	Effects	Mechanisms	References
In vivo; *In vitro*	CD38 siRNA; Oxygen deficit	C57BL/6J mice; Primary astrocytes	50 mg/kg; 10 μmol/L	i.p	OGD/R injury↓; Astrocyte activation↓; Astrocyte mitochondrial translocation↑; Restoring neuronal function↑	RET-ROS/mitochondrial translocation/ neuronal function	Jiang et al., 2021
In vivo	MCAO/R	MCAO/R mice	200 mg/kg	i.p	Cerebral infarction size↓; Compact linking protein↑; Injury of lungs↓; Intestinal injury↓; Blood-brain barrier integrity↑	PPARγ/NF-κB; Brain/lung/intestinal barrier	Liu et al., 2018
In vitro	OGD/R	BMEC	10 μmol/L		Cellular oxidative stress↓; Apoptosis↓; Autophagy↓	SQSTM1/p62; ATG5/HIF-1α	Juric et al., 2007
In vivo	Photothrombotic stroke	Sprague-Dawley rats	100 mg/kg	i.p	Ultrastructural deformation of neurons in CA1 region↓	RCBF/Cyt-C/NMDAR	Wang et al., 2017
In vivo	SAH	Sprague-Dawley rats	10 mg/kg	i.p	BBB permeability↑; Cell apoptosis and death↓; Encephaledema↓;	P53/Bax/Bcl-2/Caspase-3	Zhao et al., 2018
In vivo	dMCAO	C57BL/6 mice	5 mg/kg	i.p	Motor function of the cortex↑; Axonal regeneration↑	cAMP/PKA/CREB	Gao et al., 2020
In vivo	I/R	Sprague-Dawley rats	10 mg/kg	i.g	Neurological function↑; BBB permeability↓; Infarct size↓	Cx43/AQP4	Huang et al., 2015

(BRB), which is primarily composed of retinal microvascular endothelial cells (RMEC) and exhibits a single layer of tight connections that ensure effective barrier function (Park et al., 2017). The BRB is susceptible to hyperglycemia, aging, immune responses, and other factors that disrupts retinal homeostasis, leading to pathological changes such as apoptosis and increasing vascular permeability (Ren et al., 2024). Diabetic retinopathy is a common and specific microvascular complication of diabetes, which is found in one-third of people with diabetes is associated with an increased risk of life-threatenig systemic vascular complications, including stroke, coronary disease, and heart failure (Cheung et al., 2010). Functional blood vessel networks in the retina are formed through germination during angiogenesis, and they subsequently undergo vascular remodeling (Korn & Augustin, 2015). Inappropriate vascular remodeling is associated with disruption of barrier function and disruption of local tissue microenvironment. Many diseases are caused by disordered microvascular remodeling and abnormal functional vascular restoration, such as: proliferative diabetic retinopathy (PDR) and retinopathy of prematurity (ROP) are the most common types of retinal ischaemia induced lesions (Chen et al., 2021a). At the same time, high blood pressure also lead to a series of retinal microvascular changes called hypertensive retinopathy, which includes narrowing of the small retinal arteries, retinal bleeding, and, in severe cases, macular edema (Bhargava et al., 2012). In conclusion, retinopathy and retinal microvascular abnormalities are closely related to stroke and cerebrovascular diseases (Hughes et al., 2016). Vascular endothelial growth factor (VEGF), a potent vascular permeability factor, is involved in the pathogenesis of BRB changes, and the emergence of anti-VEGF drugs has revolutionized the treatment of diabetic retinopathy (Das et al., 2016). Ginseng is widely used for medical purposes and contains a variety of active substances, the main components extracted from ginseng are ginsenosides, which mediate many of its pharmacological effects (Lee et al., 2022).

6.2. Anti-retinopathy effect and mechanism of G-Rb_1

Diabetic retinopathy (DR) is a microvascular complication of diabetes, and more than one-third of diabetic patients have signs of DR (Ting et al., 2016). Hyperglycemia induced DR by interfering with pathways that promoting ROS formation and the glycolysis and citric acid cycles, and subsequently increased ROS damaged the mitochondrial lining, leading to increased levels of oxidative stress and decreasing DNA-binding activity of Nrf2. Studies have shown that G-Rb_1 reduced the diameter and permeability of the retina in diabetic rats, improved the nuclear translocation of Nrf2 in the retina, restored the level of GSH, and reduced the level of MDA. Therefore, G-Rb_1 regulated the anti-oxidant function of rats to reduce the degree of DR, but G-Rb_1 treatment has no effect on the blood glucose level of diabetic rats. It can be concluded that the improvement effect of G-Rb_1 on DR In diabetic rats is not related to the decrease of blood glucose (Dong et al., 2019). Retinal hypoxia and oxidative stress lead to retinal ganglion cell (RGC) apoptosis, causing irreversible neuronal damage and visual impairment in many vision-threatening diseases, including central retinal vessel occlusion, ischemic central retinal vein thrombosis, and diabetic retinopathy (Men et al., 2012). During hypoxia, production of VEGF, NO, inflammatory cytokines and increasing accumulation of intracellular Ca^{2+} eventually lead to RGC death (Nakajima et al., 2008). G-Rb_1 played a protective role in apoptosis of RGC cells through mitochondrial pathway, especially caspase protein (Liu et al., 2013). Photocell degeneration is known to be at the center of various retinal degenerative diseases (Wenzel et al., 2005). The miRNA is a small non-coding RNA molecules that regulates gene expression and plays an important role in almost all pathophysiological processes (Jonas & Izaurralde, 2015). miR-155 expression was increased in the retina after exposure to bright light. Studies have shown that G-Rb_1 and G-Rd reduced oxidative stress and inflammatory in the retina, and regulated the expression of pro-inflammatory miR-155 and its direct target, anti-inflammatory SHIP1, in LPS-stimulated RAW264.7 cells. The novel retinal protective activity of the combination of Rb1 and Rd justifies the treatment of related retinal degenerative diseases (Bian et al., 2017). The literatures on G-Rb_1 resistance to retinopathy collected from multiple databases is shown in Table 5.

7. Discussion

It is reported that China's CCVDs accounts for the first place in disease mortality, accounting for more than 40 % of the national mortality (Gaidai et al., 2023). The induction factors and development process of CCVDs is shown in Fig. 2. CCVDs are mainly caused by AS and always treated with conventional western medications to reduce the risk of heart attack and first aid (Kones, 2011). AS is a typical cardiovascular disease and an important pathophysiological basis for inducing other cardiovascular diseases (Nayor et al., 2021). At present, the treatment for AS is mainly western medicine and surgery. In recent years, due to the influence of environmental factors and the change of dietary habit, the number of patients with CCVDs has increased year by year, and there is no better treatment, which has aroused widespread concern. A large number of studies have shown that many TCMs play an important role in regulating the risk factors of CCVDs, and have protective effects in arteriosclerotic cardiovascular diseases and chronic heart diseases. There have been many reports on the use of G-Rb_1 to prevent and treat CCVDs, but no one has made a systematic summary.

Table 5
Study on G-Rb_1 anti-retinopathy model, action and mechanisms.

Type	Inducer	Animal/Cell	Dose	*In vivo* delivery mode	Effects	Mechanisms	References
In vivo	Streptozotocin	Wistar rats	40 mg/kg;	i.p	Body weight and blood sugar↓; Retinal vessels and fundus diameter↓; EBD extravasation↓; Oxidative stress level↓	Nrf2/GCLC/GCLM	Dong et al., 2019
In vitro	CoCl2/H2O2	RGC-5	10 μmol/L		Apoptosis↓; Oxidative stress level↓	Caspase-3/9/8; Mitochondrial oxidative stress	Liu et al., 2013
In vivo; *In vitro*	Bright light; LPS	$BALB^{-/-}$mice; ARPE19 and RAW264.7	65 mg/kg 100 μmol/L	i.p	Cellular oxidative stress↓; Apoptosis↓; Autophagy↓	miR-155 /SHIP1; IL-1β/IL-6/CCL2	Bian et al., 2017

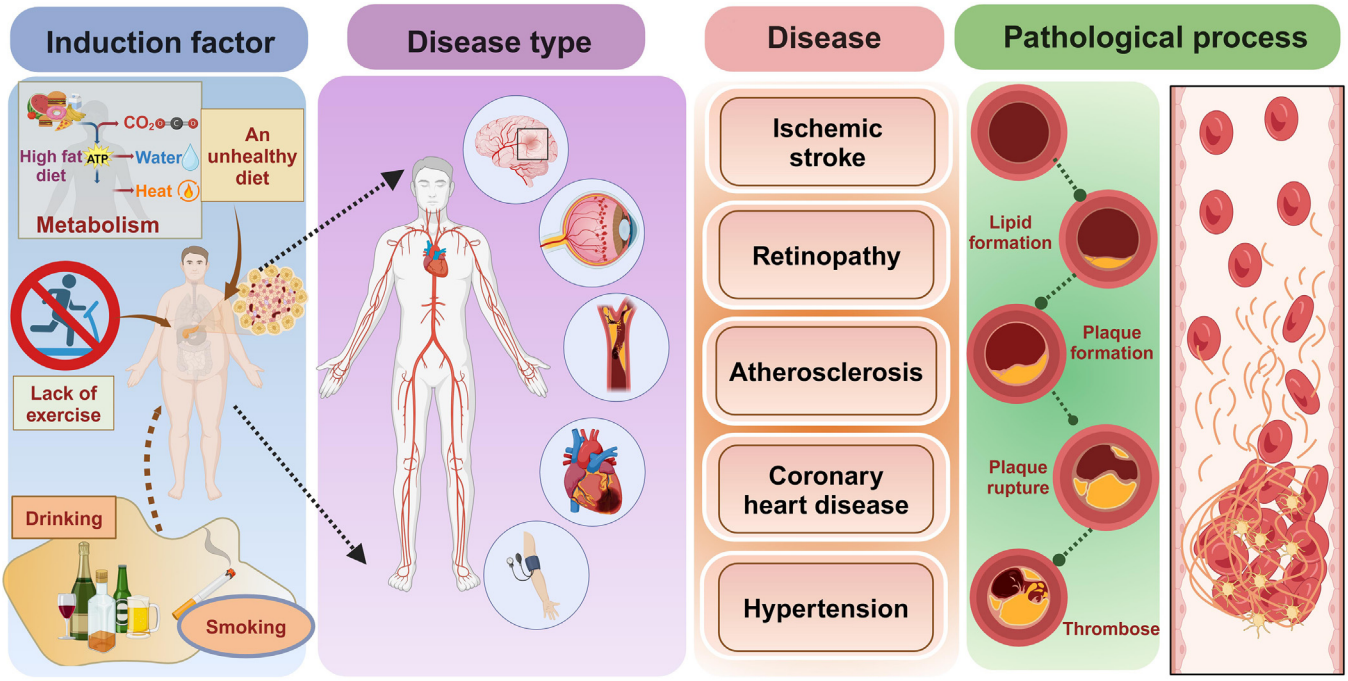

Fig. 2. Anthogenesis and development of CCVDs.

This review summarizes the mechanism of G-Rb_1 on CCVDs based on previous studies.

As the incidence of CCVDs increases year by year, it has led many to advocate for more widespread use of statins for rapid treatment. However, they found only a slight reduction in the risk of events CCVDs after statin use. In addition, statins caused many side effects, which greatly limited their net benefit (Durai & Redberg, 2022). It has been concluded that statins aggravated severe hepatotoxic damage and were associated with cholestatic damage in the body (Russo et al., 2009). However, it has been reported that G-Rb_1 alleviated acute liver injury caused by acetaminophen (APAP), showing significant liver protection (Ren et al., 2019). Muscle is also commonly reported as an adverse event associated with statin therapy, and muscle pain in patients with CCVDs is associated with statin use (Pergolizzi et al., 2020). For clinical use, 15 cases of muscle rupture associated with statin use were identified in the Pharmacovigilance Center database in the Netherlands (Ekhart et al., 2016). G-Rb_1 improved insulin sensitivity of muscle cells through different signaling pathways and played a role in muscle protection (Tabandeh et al., 2017). As a natural product isolated from ginseng, the importance of G-Rb_1 in the treatment of human diseases has been fully demonstrated. Literature reviews showed that the improvement of G-Rb_1 on CCVDs involves multiple signaling molecules, multiple pathways, and presents the characteristics of multi-target and multi-action. Although G-Rb_1 is widely favored by patients and researchers due to its rich content, simple preparation and small toxic side effects, its large molecular weight makes it difficult to be absorbed by the human body and its bioavailability is low. Therefore, new drug formulations of G-Rb_1 such as G-Rb_1 nanocapsule, G-Rb_1-paclitaxel self-assembled nanoparticles, G-Rg_3-G-Rb_1 assembled nanoparticles can well solve the problem of low bioavailability, and achieve a better effect of slow release (Liu et al., 2020; Lu et al., 2023; Zuo et al., 2022). This form of drug formulation is currently widely used in studies of G-Rb_1 in the treatment of arthritis and anti-tumor, but its effect on CCVDs has not been reported.

The TCM prescriptions, which rich in G-Rb_1 are the concrete embodiment of the clinical application of G-Rb_1. Shengmai San (SMS) originated in the Jin and Yuan dynasties of China, composed of *ginseng*, *Ophiopogon japonicus* (L. f.) Ker Gawl. and *Schisandra chinensis* (Turcz.) Baill., which was a first-aid prescription for TCM in the past dynasties, and now it is found that G-Rb_1 is its main component (Zhan et al., 2019). The mechanism summary of G-Rb_1 against CCVDs was shown in Fig. 3. Studies have shown that SMS

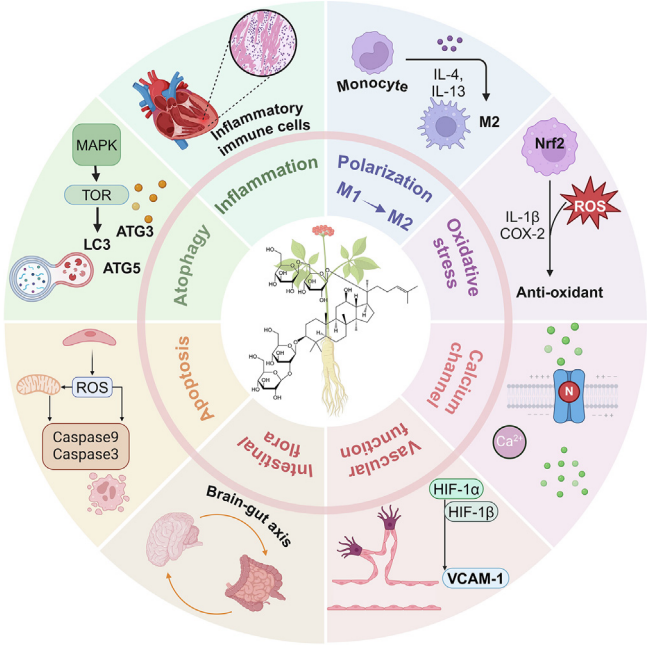

Fig. 3. Mechanism of G-Rb_1 against CCVDs.

improved AS, reduced serum cholesterol levels and aortic plaque area in APOE$^{-/-}$mice, and the mechanism is related to downregulation of lysophosphatidylcholine (Wang et al., 2021). Wang et al. verified the cardioprotective effect of SMS on rats with chronic heart failure (CHF). The model of CHF was constructed by ligation of the left anterior branch tubular artery of rats. Oral administration of SMS could restore the cardiac function of rats and reduce cardiac histological damage. Metabolomics analysis showed that the therapeutic effect of SMS on CHF rats was influenced by the metabolic pathway of linoleic acid (Wang et al., 2022). Compound Danshen dropping pills (CDDP) is a Chinese medicine prescription for prevention and treatment of various CCVDs. G-Rb$_1$, tanshinol and salvianolic acid are its main components (Yang et al., 2015). Yang et al. studied the effect of CDDP on vascular calcification in APOE$^{-/-}$mice. CDDP reduced calcification of the vascular intima in APOE$^{-/-}$mice with AS lesions, and it was determined that CDDP inhibited the Wnt/β-catenin pathway by up-regulating the expression of Wnt upstream inhibitors DKK1 and LRP6. Thus, the expression of osteoblast transformation markers (ALP, OPN, BMP2 and RUNX2) was reduced, which played a vascular protective role (Yang et al., 2024). At the same time, the studies showed that CDDP improved the apoptosis of retinal cells (Zhang et al., 2018), high altitude hypoxia injury (Hu et al., 2021) and myocardial infarction (Zhang et al., 2024). TCM compounds are the main form and means of clinical treatment in TCM, and the core of research and development of TCM by modern scientific and technological means. However, the basic research on its mechanism of action and pharmacodynamic substances lacks full scientific explanation, and few innovative medicines of TCM compounds with outstanding curative effect are applied to clinical research. In recent years, the emergence of the concept of interdisciplinary integration has provided new ideas and models for the development of TCM.

G-Rb$_1$, a bioactive component of *ginseng*, emerges as a promising candidate due to its diverse pharmacological properties targeting key pathological processes implicated in the progression of CCVDs. Here we present the latest findings, advances, and research on the therapeutic value of G-Rb$_1$ in several CCVDs, such as: AS, hypertension, CHD, IS, periocular microvascular retinopathy. The main molecular mechanisms involved include anti-inflammatory, anti-oxidant, angiogenesis, vascular remodeling, regulation of autophagy and so on. Despite the promising preclinical findings, further research is warranted to translate the therapeutic potential of G-Rb$_1$ into clinical applications. Clinical trials are needed to evaluate the efficacy, safety, and optimal dosage regimens of G-Rb$_1$ in CCVDs patients. Moreover, elucidating the pharmacokinetic profile and bioavailability of G-Rb$_1$ will facilitate its clinical development and therapeutic use.

CRediT authorship contribution statement

Yueqin Song: Data curation, Writing – original draft. **Chen Chen:** Writing – review & editing. **Wei Li:** Formal analysis, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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