REVIEW
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Pharmacological properties and mechanisms of ginsenoside Rg1 against acute kidney injury

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Author contributions

Zhang YX researched the literature, organized information, and drafted the original manuscript. Li XF and Zhang JY guided, supervised and revised the manuscript. All authors contributed to the article and approved the final submitted version.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

AKI, acute kidney injury; AMPK, AMP-activated protein kinase; CoQ, coenzyme Q; ER, endoplasmic reticulum; FSP1, ferroptosis-suppressor-protein 1; GBM, glomerular basement membrane; G-Rg1, ginsenoside Rg1; HO-1, heme oxygenase-1; MDA, malondialdehyde; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-κB; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; TGF-β1, transforming growth factor-β1; UUO, unilateral ureteral obstruction; IL, interleukin; LPS, lipopolysaccharide; GSH, glutathione; GN, glomerular nephritis; TNF, tumor necrosis factor; NAD(P)H, nicotinamide adenine dinucleotide phosphate hydride; MPC5, mouse podocyte clone-5; LC3-I, microtubule-associated protein 1 light chain 3 I.

Citation

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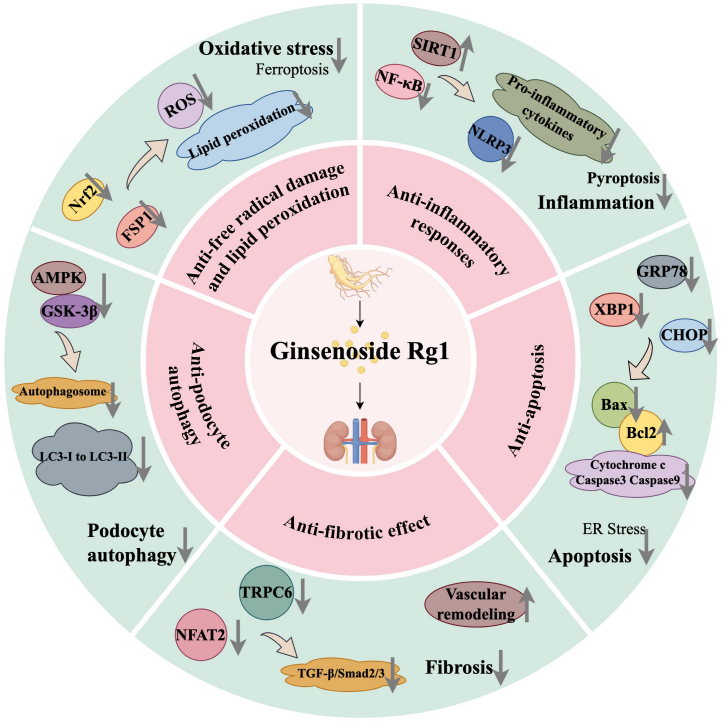
Abstract

Acute kidney injury is a common complication that can arise from improper medication use, mechanical injury, and other underlying conditions, potentially leading to life-threatening situations in severe cases. Ginsenoside Rg1, a major protopanaxatriol saponin, exhibits pharmacological activities such as antioxidant, anti-inflammatory, and anti-tumor effects, demonstrating significant nephroprotective properties in various renal injury models. This article reviews the mechanisms and recent research advancements of ginsenoside Rg1 in preventing acute kidney injury, focusing on five key areas: antioxidant, anti-inflammatory, anti-apoptotic, anti-podocyte autophagy, and anti-fibrotic activities. These insights provide a valuable foundation for its further development and application.

Keywords: ginsenoside Rg1; kidney; oxidative stress; inflammation; apoptosis; mechanism



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Highlights

1. Ginsenoside Rg1 (G-Rg1) demonstrated remarkable protective effects across various kidney injury models.
2. This review explored the potential of G-Rg1 in managing kidney injury through five critical mechanisms.
3. We also summarized the relevant signaling pathways through which G-Rg1 exerts its protective effects.

Medical history of objective

G-Rg1 is primarily derived from the dried roots of *Panax ginseng* C.A. Meyer, a plant documented in the Chinese book *Shennong's Classic of Materia Medica* (Shennong, 200 C.E. and 250 C.E.). Ginseng has long been valued in traditional medicine for its ability to replenish vitality and improving strength. The active compounds known as ginsenosides are the key contributors to its therapeutic effects. Among them, G-Rg1 is one of the most abundant and potent components, demonstrating a wide range of beneficial effects, including boosting immunity, combating aging, and protecting blood vessels.

Background

Acute kidney injury (AKI) is a common clinical complication characterized by a rapid decline in kidney function. This decline is typically marked by a reduction in the estimated glomerular filtration rate, alongside the accumulation of serum creatinine and urea nitrogen [1]. Various risk factors contribute to the onset of AKI, including drug-induced nephrotoxicity, infections, ischemia-reperfusion injury, and other tissue damage [2–5]. Research has identified several core mechanisms underlying AKI, including oxidative stress, inflammation, mitochondrial damage, autophagy disorder, and immune dysfunction [6–10]. Recent studies have also highlighted the crucial role of gut microbiota in the development and progression of AKI. For instance, AKI has been shown to disrupt gut microbiota balance, leading to significant increases in *Bifidobacterium* and *Bacteroides*, while *Escherichia coli* and *Streptococcus* levels decrease [11]. This microbial imbalance results in a reduction of probiotics, particularly *Bifidobacterium*, which in turn lowers the expression of tight junction proteins such as zonula occludens-1 and occludin, increasing intestinal permeability [12, 13]. The disrupted gut microbiota further exacerbates AKI by promoting the excessive secretion of uremic toxins like indoxyl sulfate and p-cresol sulfate, which damage renal tubular cells [14]. Additionally, the loss of beneficial short-chain fatty acids, normally produced by a healthy gut microbiota, accelerates the deterioration of kidney function [15]. The incidence of AKI continues to rise each year, increasing the risk of chronic kidney disease and potentially leading to end-stage renal disease if not promptly addressed. This progression poses a significant threat to patients' lives [16–18].

Ginseng (*Panax ginseng* C.A. Meyer), often referred to as the "king of all herbs," is a renowned perennial plant in the Araliaceae family, prized for its medicinal properties primarily due to its active compounds, ginsenosides [19]. Ginsenosides possess a wide range of pharmacological effects, including neuroprotective, anti-aging, antioxidant, anti-inflammatory and anti-cancer properties [20–24]. Significant progress has been made in the research and development of ginsenosides, particularly in the extraction, isolation, and industrial preparation of individual monomers [25]. Ginsenosides have been investigated in numerous clinical studies, including trials for cancer, diabetes, chronic kidney disease, hypertension, and acute ischemic stroke [26–32]. Among these, G-Rg1 is one of the most abundant and potent saponins [33]. Research has demonstrated that G-Rg1 offers strong protective effects against various types of kidney injuries [34–36]. Given these promising results, G-Rg1 is emerging as a potential treatment for kidney injury. Therefore, it is crucial to summarize the protective effects and underlying molecular mechanisms of G-Rg1 in different forms of kidney injury.

Most current studies focus primarily on the therapeutic effects of G-Rg1 in in vivo and in vitro models of renal injury. In contrast, this review offers a comprehensive summary of the pharmacology of G-Rg1, the latest research on its molecular mechanisms in combating kidney damage, and relevant clinical studies. By consolidating this information, the review aims to inspire further research and provide a solid scientific foundation for the clinical application of G-Rg1 in medicine.

Pharmacological properties

G-Rg1, serving as a key quantitative measure of ginseng efficacy, is one of the major monomer saponins of ginsenosides, which can also be identified by its aglycone structure, protopanaxatriol [37]. The molecular formula of G-Rg1 is $C_{42}H_{72}O_{14}$ and the structure is presented in Figure 1. G-Rg1 presents as a white powder with high solubility in water, methanol, and ethanol, while remaining insoluble in ether and benzene [38].

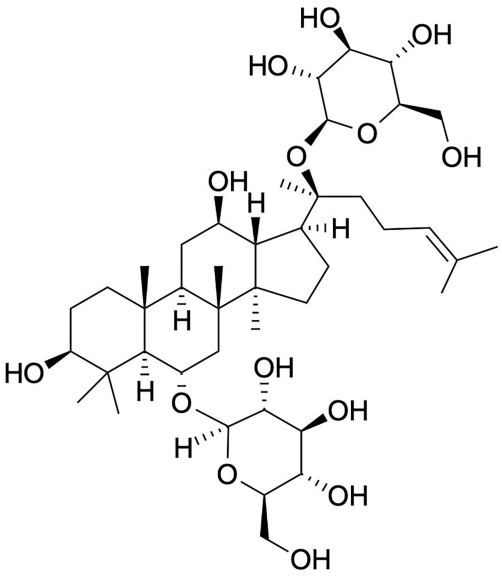

Figure 1 The chemical structure of G-Rg1

Previous studies have found that G-Rg1 shows a wide range of pharmacological effects on various diseases, including hepatic diseases, cardiovascular diseases, neurological diseases, diabetes, lung diseases, digestive system disorders, cancer, and other diseases [39–85]. We briefly introduce the protective effects of G-Rg1 on various diseases in Figure 2.

Recent evidence indicates that G-Rg1 plays a significant role in protecting against renal injuries. It helps mitigate maladaptive kidney repair and slows the progression from AKI to chronic kidney disease through its antioxidative, anti-apoptotic, anti-inflammatory, and anti-fibrotic effects, as well as angiogenesis [34–36, 86–93]. G-Rg1 has been shown to reduce renal fibrosis in mice with diabetic nephropathy and inhibit renal interstitial fibrosis in a rat model of unilateral ureteral obstruction (UUO) [92, 93]. Additionally, it significantly improves renal injury induced by cyclosporine A in rats and D-galactose in mice [89, 94]. A summary of G-Rg1's nephroprotective effects across various renal injury models is provided in Table 1 [34–36, 59, 86, 87, 89, 91, 95–100].

Pharmacokinetics

G-Rg1 is primarily absorbed in the intestine and is significantly influenced by gastric juice, intestinal flora, and liver activity [101, 102]. These factors can affect the gastric acid pH, liver enzymes, and intestinal transporters, leading to lower bioavailability of G-Rg1 [103]. Pharmacokinetic studies in rats have shown that G-Rg1 follows a two-compartment model, characterized by rapid absorption and relatively fast elimination [104]. It is reported that G-Rg1 can be further decomposed into ginsenosides Rh1 and F1 under the influence of gut microbiota, and finally metabolically converted into 20(S)-protopanaxatriol, which exhibits enhanced biological activity in vivo [105–107]. Although the concentration of G-Rg1 in the blood is relatively low, its slow metabolism means it can still be detected in the bloodstream up to 24 h after gavage administration.

Compared to gavage administration, the mean residence times for G-Rg1, Rh1, and F1 following intravenous administration are 1.92, 5.99, and 7.13 h, respectively. This indicates that G-Rg1 is eliminated from the body relatively quickly, whereas its metabolites persist for a longer duration. The area under the concentration-time curve reveals that a larger proportion of G-Rg1 remains in its original form after intravenous administration, with a relatively smaller proportion being metabolized [108]. Overall, whether administered orally or intravenously, G-Rg1's metabolites are widely distributed throughout the body, maintain high concentration levels, and are eliminated more slowly.

Molecular mechanisms of G-Rg1 against kidney injury

Anti-free radical damage and lipid peroxidation

Oxidative stress is central to the pathogenesis of kidney injury [109]. When the kidney is exposed to harmful stimuli, such as certain drugs, it produces a significant amount of reactive oxygen species (ROS) and reactive nitrogen species. This imbalance between oxidation and antioxidation leads to damage of lipids, proteins, and DNA, ultimately triggering apoptosis and renal injury [110]. Markers of oxidative stress can help assess the extent of damage. For instance, elevated levels of malondialdehyde (MDA), a byproduct of lipid peroxidation, indicate the onset of renal injury. Additionally, decreased activity of key antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GSH-Px) exacerbates oxidative stress [22]. The Nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element signaling pathway plays a crucial role in managing oxidative stress. Activation of this pathway leads to the expression of protective genes like heme oxygenase-1 (HO-1) and nicotinamide adenine dinucleotide phosphate hydride (NAD(P)H) quinone oxidoreductase 1, which help counteract oxidative damage [111, 112]. Research shows that G-Rg1 can alleviate renal injury caused by D-galactose in mice by improving renal function and reducing tissue senescence. This effect is associated with increased activities of SOD and GSH-Px and reduced MDA levels [89]. Additionally, G-Rg1 has been found to protect against rhabdomyolysis-induced AKI by suppressing ROS and MDA accumulation in serum and renal tissue. The protective mechanism may involve the activation of Nrf2 and its target HO-1, as well as the retention of Nrf2 in the nucleus [86].

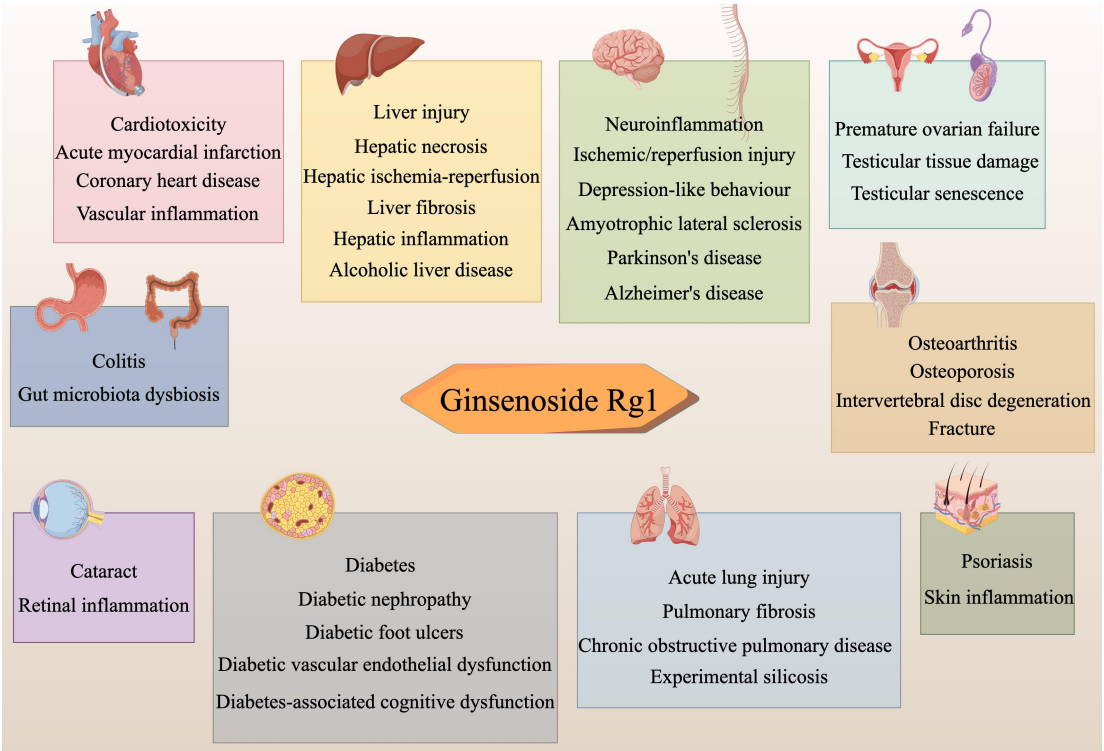

Figure 2 Overview of the potential therapeutic role of G-Rg1 across different organ systems

Table 1 Nephroprotective activity of G-Rg1 in vivo and in vitro

Disease or disorder	Model	Treatment	Outcome	References
Chronic renal injury	Lipopolysaccharide (LPS)-induced in mice	1, 5 and 10 mg/kg G-Rg1 intragastrically	Ameliorate LPS-induced chronic kidney injury and renal fibrosis	[34]
Obstructive nephropathy	UUO-induced in rats	50 mg/kg G-Rg1 intraperitoneally	Reverse UUO-induced renal fibrosis	[35]
Diabetic nephropathy	Streptozotocin-induced in rats	50 mg/kg G-Rg1 intragastrically	Alleviate oxidative damage and renal fibrosis	[36]
Diabetic nephropathy	High-fat diet and streptozotocin-induced in mice	1, 5 and 10 mg/kg G-Rg1 intragastrically	Ameliorate renal lipid accumulation, pathological damage and glomerular fibrosis in type 2 diabetes mellitus mice	[59]
Rhabdomyolysis-induced AKI	Glycerol-induced in rats; H_2O_2-induced in human embryonic kidney-293 cells	10 and 20 mg/kg G-Rg1 orally; 20 and 40 μM G-Rg1 exposed to human embryonic kidney-293 cells	Mitigate the renal dysfunction, tubular necrosis and apoptotic cell death	[86]
Aldosterone-induced injury	Aldosterone-induced in mouse podocyte clone-5 (MPC5) cell line	80 ng/mL G-Rg1	Relieve oxidative damage and inhibit podocyte autophagy	[87]
Subacute murine renal damage	D-galactose-induced in mice	20 mg/kg G-Rg1 intraperitoneally	Antagonise D-galactose-induced renal damage and aging state	[89]
Kidney aging-related glomerular fibrosis	Senescence accelerated mouse prone 8 mice	5 and 10 mg/kg G-Rg1 intragastrically	Delay kidney aging and inhibit aging-related glomerular fibrosis	[91]
Anti-glomerular basement membrane (GBM) glomerular nephritis (GN)	IL-1β treated podocytes; anti-GBM GN mice model	80 ng/mL exposed to podocytes	Attenuate IL-1β-induced inflammation and apoptosis in podocytes and improve anti-GBM GN injury in vivo	[95]
Sepsis-associated AKI	LPS-induced in mice	200 mg/kg G-Rg1 intraperitoneally	Ameliorate LPS-induced AKI and suppress renal inflammation, apoptosis, and oxidative stress in mice	[96]
Chronic kidney disease	Angiotensin II-induced in MPC5 cell line	80 ng/mL G-Rg1	Relieve Ang II-induced autophagy in podocyte	[97]
Membranous nephropathy	Zymosan-activated mouse serum-induced in MPC5 cell line	40 ng/mL G-Rg1	Protect foot processes of podocytes, inhibit the damage of F-actin and decrease ROS level	[98]
Hypertension	Spontaneously hypertensive rats	5, 10 and 20 mg/kg G-Rg1 intraperitoneally	Reduce the thickening of the GBM and protect the ultra-structure integrity of kidney	[99]
Aldosterone-induced injury	Aldosterone-induced in normal rat kidney-52E cell line	80 ng/mL G-Rg1	Relieve oxidative damage and abnormal autophagy in renal tubular cells	[100]

AKI, acute kidney injury; GBM, glomerular basement membrane; LPS, lipopolysaccharide; GN, glomerular nephritis; IL, interleukin; ROS, reactive oxygen species; UUO, unilateral ureteric obstruction; G-Rg1, ginsenoside Rg1; MPC5, mouse podocyte clone-5.

Ferroptosis is a distinct form of iron-dependent programmed cell death, characterized by iron overload, accumulation of reactive ROS, lipid peroxidation, and mitochondrial contraction [113]. It is regulated by various molecular mechanisms, including antioxidant signaling pathways [114]. Research has shown that ferroptosis is linked to the progression of several renal diseases, such as diabetic nephropathy and hypertensive nephropathy [115, 116]. In ferroptosis, Fe^{2+} loading triggers the process, while oxidative stress and lipid peroxidation drive the progression of renal injury. Glutathione peroxidase 4 (GPX4) is crucial in ferroptosis, acting as a key reductase to counteract lipid peroxidation and playing a role in oxidative stress, inflammation and autophagy [117–119]. Ferroptosis-suppressor-protein 1 (FSP1) inhibits ferroptosis inhibitor by reducing coenzyme Q (CoQ) to CoQH2, which neutralizes excess ROS and prevents lipid peroxidation [120]. Guo et al. found that G-Rg1 significantly alleviates sepsis-induced kidney injury by reducing iron and MDA levels while increasing lipid ROS, GSH, GPX4, and FSP1 levels. These effects are likely linked to the activation of the FSP1-CoQ10-NAD(P)H signaling pathway [88, 121].

Anti-inflammatory responses

In response to certain noxious stimuli to renal tissue, inflammatory factors such as tumor necrosis factor (TNF), interleukin-1 (IL-1) and IL-6 are released in excess. Neutrophils and macrophages are recruited to the damaged areas, leading to the upregulation of adhesion molecules on renal endothelial cells and increased vascular permeability. Additionally, Toll-like receptors and complement binding increase, causing damage to renal parenchymal cells and a rapid decline in kidney function [7, 122]. Studies have shown that the nuclear factor-κB (NF-κB) pathway is involved in the induction of inflammatory responses in kidney injury. When activated, NF-κB signaling leads to the degradation of IκBα, leading to the phosphorylation of p65 and the subsequent synthesis and accumulation of pro-inflammatory cytokines [123, 124]. G-Rg1 has been shown to significantly reduce levels of inflammatory factors such as IL-6, IL-1β and TNF-α in serum. It upregulates the expression of SIRT1 and IκBα while downregulating the expression of p-NF-κB p65/NF-κB p65 in experimental models of sepsis-induced AKI. These findings suggest that G-Rg1 may alleviate sepsis-induced kidney injury through the SIRT1/NF-κB signaling pathway [96]. Furthermore, oxidative stress can also activate inflammatory responses by releasing inflammatory factors and promoting the deposition of inflammatory cells in renal tissue [36, 100]. Guo et al. demonstrated that G-Rg1 could attenuate inflammation and apoptosis induced by IL-1β in

podocytes. This effect can be reversed by the Nrf2 inhibitor ML385, indicating that G-Rg1 may improve GN by activating the Nrf2 signaling pathway [95].

Additionally, studies have shown that the activation of inflammasomes can also induce pyroptosis, which is partly responsible for the progression of kidney injury [125]. Unlike apoptosis, which is regulated by genetic programs, pyroptosis is a specific form of programmed necrotic cell death only in response to external stimuli and is characterized by cell swelling, membrane rupture and the release of pro-inflammatory cytokines, ultimately leading to inflammatory responses [126]. Wang et al. found that G-Rg1 could inhibit the generation of NOD-like receptor family protein 3 (NLRP3) inflammasomes in podocytes. This inhibition significantly reduces pyroptosis in podocytes under hyperlipidemic conditions and in diabetic nephropathy rats. The protective effect of G-Rg1 may be mediated through the downregulation of the mTOR/NF-κB signaling pathway [127].

Anti-apoptosis

Apoptosis, a genetically regulated process of cell death, is pivotal in renal injuries. This process primarily involves the death receptor pathway, the mitochondrial pathway, and the endoplasmic reticulum (ER) pathway [128–131]. G-Rg1 has been shown to mitigate apoptosis by addressing mitochondrial dysfunction and ER stress. The Bcl-2 family of proteins regulates mitochondrial permeability, leading to mitochondrial swelling, membrane rupture, and the release of cytochrome c. This process results in the formation of apoptotic bodies and the activation of caspases [132, 133]. ER stress, characterized by protein misfolding and prolonged unfolded protein responses, can also trigger apoptotic caspases and induce cell death. Chang et al. demonstrated that G-Rg1 reduces the expression of ER stress-related proteins such as C/EBP-homologous protein (CHOP), 78-kDa glucose-regulated protein (GRP78), and X-box binding protein-1 (XBP1), as well as apoptosis-related proteins including Bax, Bcl-2, cytochrome c, caspase 3, and caspase 9, along with nuclear p53. These findings suggest that G-Rg1 may alleviate glycerol-induced renal injury by inhibiting ER stress and apoptosis [86].

Anti-podocyte autophagy

Podocytes are highly specialized epithelial cells crucial for the glomerular filtration barrier, forming a key component of the GBM [134]. Autophagy, a lysosomal degradation pathway, plays a vital role in maintaining podocyte homeostasis by eliminating misfolded proteins and damaged organelles. However, dysfunction in autophagy can lead to podocyte injury and death, significantly contributing to the progression of nephropathies such as AKI, diabetic nephropathy, and polycystic kidney disease [9, 135]. Podocyte injury is associated with various kidney diseases, including focal segmental glomerulosclerosis and minimal change disease [136]. During such injuries, autophagosomes form and express autophagy-related proteins like microtubule-associated protein 1 light chain 3 I (LC3-I), LC3-II, and Beclin-1. These autophagosomes fuse with lysosomes to degrade oxidized proteins and damaged organelles, potentially leading to nephrotoxicity [97]. Autophagy is regulated by AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR). AMPK, a key regulator of cellular energy metabolism, positively influences autophagy, whereas mTOR, which regulates cell growth and proliferation, inhibits it. Thus, the AMPK/mTOR axis mediates autophagy through a mutually antagonistic mechanism [137–139]. Research has shown that G-Rg1 significantly reduces the conversion of LC3-I to LC3-II and the production of autophagosomes in MPC5 mouse podocytes treated with aldosterone, indicating its potential to alleviate aldosterone-induced podocyte autophagy [87]. Additionally, G-Rg1 inhibits autophagosome formation and reduces the expression of autophagy-related proteins LC3-I, LC3-II, and Beclin-1, as well as p-AMPK/AMPK, p-GSK-3β/GSK-3β, and p-P70S6K/P70S6K in damaged podocytes. These findings suggest that G-Rg1 can effectively mitigate angiotensin II-induced podocyte autophagy, likely through regulation of the AMPK/mTOR/PI3K signaling pathway [97].

Anti-fibrotic effect

Renal fibrosis is a common pathological process of maladaptive repair following various kidney injuries. It is characterized by the infiltration of inflammatory cells, excessive accumulation of extracellular matrix proteins, and the proliferation and activation of myofibroblasts. One mechanism involved in renal fibrosis is epithelial-mesenchymal transition, which is primarily initiated by transforming growth factor-β1 (TGF-β1) [140, 141]. Activated TGF-β1 binds to its receptors transforming growth factor β receptor I (TβR-I) and TβR-II on the cell membrane, which then activates and phosphorylates downstream receptors such as Smad2 and Smad3. This signaling cascade results in decreased expression of E-cadherin in epithelial cells and increased expression of fibroblast-specific protein 1 and α-smooth muscle actin (α-SMA), leading to kidney damage and fibrosis [142–145]. Li et al. demonstrated that G-Rg1 alleviates renal fibrosis induced by UUO in rats. G-Rg1 regulates the overexpression of TGF-β1 and α-SMA and reverses the inhibition of E-cadherin on the cell membrane through the Klotho/TGF-β1/Smad signaling pathway [35]. Similarly, Han et al. found that G-Rg1 reduces renal damage, lipid deposition, and glomerular fibrosis in type 2 diabetes mellitus mice. This effect is associated with the downregulation of TGF-β/Smad2/3 signaling, mediated through the inhibition of the TRPC6/NFAT2 pathway [59].

Hypertension is a well-established risk factor for renal vascular diseases. It can cause thickening of the GBM and mesangium, as well as disrupt the arrangement of podocytes, ultimately leading to renal fibrosis. Chen et al. found that G-Rg1 helps facilitate renal vascular remodeling in cases of spontaneous hypertension, thereby preserving the renal vascular structure and function [99].

Clinical applications

G-Rg1 is often used as an adjuvant in various traditional Chinese medicine formulas, particularly in conjunction with chemotherapy drugs [146–148]. Despite the growing understanding of G-Rg1's mechanisms of action against kidney damage at the animal and cellular levels, clinical data remains limited, which hampers the development of related renoprotective therapies. Aidi injection, which contains extracts from *Mylabris*, *Panax ginseng* C.A. Meyer, *Astragalus membranaceus* (Fisch.) Bge. *var. mongholicus* (Bge.) Hsiao, and *Eleutherococcus senticosus*, is commonly used for treating malignant tumors. Its main active ingredients include cantharidin, ginsenoside, astragaloside, and eleutheroside E. [149]. Reports indicate that Aidi injection can significantly enhance chemotherapy efficacy in patients with advanced non-small cell lung cancer while also reducing its toxic effects, including those on renal function [150].

Safety evaluation

G-Rg1, a principal active component of ginseng – a traditional Chinese herb celebrated for its tonic effects – is generally considered safe for medical use. Although clinical studies are relatively sparse, preclinical research has consistently demonstrated G-Rg1's safety. In animal studies, doses up to 200 mg/kg have been administered without causing noticeable weight loss or significant organ toxicity [151, 152].

Discussion

The renal protective effects of G-Rg1 are associated with several potential mechanisms of action (Figure 3): the activation of Nrf2/HO-1 signaling pathway to ameliorate oxidative stress; the upregulation of FSP1-CoQ10-NAD(P)H signaling pathway to reduce lipid peroxidation and ferroptosis; the regulation of SIRT1/NF-κB and mTOR/NF-κB pathway to mitigate inflammation; the inhibition of GRP78/PERK/CHOP pathway to attenuate ER stress and apoptosis; the regulation of AMPK/mTOR/PI3K signaling pathway to alleviate podocyte autophagy; the inhibition of TRPC6/NFAT2 signaling pathway to alleviate renal fibrosis [59, 86, 88, 90, 96, 97, 121, 127].

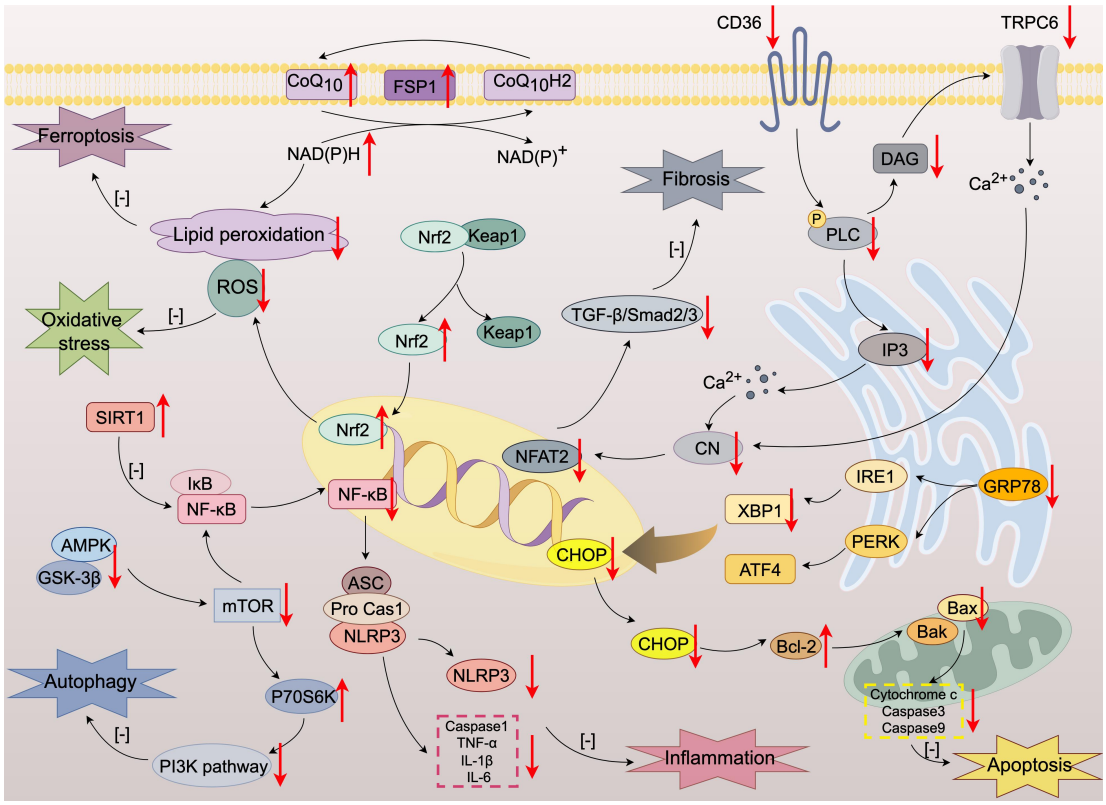

Figure 3 Functional mechanisms and targets of G-Rg1 against kidney injury. AMPK, AMP-activated protein kinase; ASC, apoptosis-associated speck-like protein containing CARD; CD36, cluster of differentiation 36; CHOP, C/EBP-homologous protein; CN, calcium-regulated neurophosphatase; DAG, diacyl glycerol; GRP78, 78-kDa glucose-regulated protein; GSK-3β, glycogen synthase kinase 3β; IκB, inhibitor of NF-κB; IL, interleukin; IP3, inositol triphosphate; IRE1, inositol-requiring enzyme 1; mTOR, mammalian target of rapamycin; NFAT2, nuclear factor of activated T cells 2; NF-κB, nuclear factor κB; NLRP3, NOD-like receptor family protein 3; Nrf2, nuclear factor erythroid 2-related factor 2; P70S6K, 70 kDa ribosomal S6 kinase; PERK, protein kinase RNA-like endoplasmic reticulum kinase; PLC, phospholipase C; PI3K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species; SIRT1, Sirtuin 1; TGF-β, transforming growth factor-β; TNF, tumor necrosis factor; TRPC6, transient receptor potential cation channel 6; CoQ, coenzyme Q; FSP1, ferroptosis-suppressor-protein 1; XBP1, X-box binding protein-1; NAD(P)H, nicotinamide adenine dinucleotide phosphate hydride; ATF4, activating transcription factor 4.

G-Rg1 stands as a promising candidate for preventing kidney injury, yet there remain some problems in the application and research limitations. As one of the most bioactive constituents extracted from ginseng, G-Rg1 is a natural source that has been extensively studied for their renal protection potential. This review highlights the protective effect of G-Rg1 in various kidney injury models. Natural extracts and their bioactive compounds exhibit multi-targeted mechanisms of action with minimal side effects, making them advantageous for renal protection. However, despite their promising preclinical results, the poor bioavailability of natural products often impede their clinical translation [153]. The research limitations refer to obsolescence of the detected signaling pathways, lack of multicenter large-sample clinical trials and G-Rg1 target screening based on high-throughput methods. Future research on G-Rg1 and kidney injury should focus on the following areas.

(I) Conduct in-depth research into the key molecular targets of G-Rg1 renoprotective effects.

(II) Explore alternative methods of administration to enhance bioavailability and consider drug absorption rates and potential side effects.

(III) Develop and conduct clinical trials to establish the optimal timing and dosage for effective treatment, moving from basic research to practical clinical applications.

Conclusion

In summary, growing evidence highlights G-Rg1 as having significant renoprotective effects in animal and cell models. Recent research has elucidated its multitarget and multipathway mechanisms of action, providing new insights into its potential for treating and preventing kidney injury.

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