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Review

The potential therapeutic role of ginsenosides on fibrosis-associated diseases: a review on molecular mechanisms and call for further research

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ABSTRACT

Fibrosis is characterized as an aberrant reparative process involving the direct replacement of damaged or deceased cells with connective tissue, leading to progressive architectural remodeling across various tissues and organs. This condition imposes a substantial burden, resulting in considerable morbidity and mortality. Ginseng (*Panax ginseng* C. A. Meyer), renowned for its medicinal properties, has been incorporated as a key component in Chinese patent medicines to mitigate fibrotic diseases. Ginsenosides, the primary bioactive compounds in ginseng, have garnered significant attention. Over the past five years, extensive research has explored the pharmaceutical potential of ginsenosides in diverse organ fibrosis conditions, including liver, myocardial, renal, and pulmonary fibrosis. Studies have elucidated that ginsenosides demonstrate potential effects on inflammatory responses stemming from parenchymal cell damage, myofibroblast activation leading to extracellular matrix (ECM) production, and myofibroblast apoptosis or inactivation. Additionally, potential downstream targets and pathways associated with these pathological processes have been identified as being influenced by ginsenosides. This review presents a comprehensive overview of the efficacious treatments utilizing ginsenosides for various tissue fibrosis types and their potential antifibrotic mechanisms. Furthermore, it offers a reference for the development of novel candidate drugs for future organ fibrosis therapies.

1. Introduction

Fibrosis is a pathological condition characterized by excessive accumulation of extracellular matrix (ECM) proteins in and around damaged or dead tissue, potentially leading to permanent scarring, organ dysfunction, and mortality [1, 2]. In developed nations, fibrotic pathologies account for approximately half of all deaths [3, 4]. Common fibrosis-associated diseases include non-alcoholic steatohepatitis (NASH), cirrhosis, chronic kidney disease, myocardial infarction (MI), heart failure (HF), diabetes mellitus, idiopathic pulmonary fibrosis, and scleroderma [5, 6]. Regardless of the affected tissue or organ and specific etiology, fibrosis represents the final common pathological outcome of these chronic diseases [7]. Fibrosis is often diagnosed at an advanced stage when extensive scarring has already compromised organ function. This late detection significantly contributes to the poor prognosis and high mortality rate among patients with fibrosis [8]. Various triggers can contribute to progressive fibrotic disease development, including genetic disorders, persistent infections, recurrent exposure to toxins, irritants or smoke, chronic autoimmune inflammation, MI, elevated serum cholesterol, and poorly managed diabetes mellitus and hypertension [2]. Despite the high mortality and morbidity associated with fibrosis, effective therapies are limited, particularly those targeting fibrogenesis specifically [9]. Recent discoveries have revealed potential therapeutic opportunities, especially in metabolic regulation [5], neutralization of matrix metalloproteinases (MMPs)/lysyl oxidase activity [10], inhibitory effects of fibroblast growth factor 2 on fibroblasts [4], inhibition of transforming growth factor β1 (TGF-β1), and antagonism of cytokine production [11]. However, current available treatments merely delay the fibrotic process and cannot reverse or halt fibrosis progression, leaving organ transplantation as the sole option for patients with advanced fibrosis [8]. Furthermore, the excessive accumulation of ECM components increases tissue stiffness, creating an inaccessible microenvironment that impedes drug accumulation, distribution, and efficacy [12]. These factors underscore the necessity for a more comprehensive understanding of fibrogenesis pathogenesis and the translation of this knowledge into novel treatments [9].

The fibrogenic response comprises four primary phases. The initial phase involves the commencement of the response triggered by primary organ injury. Endothelial damage prompts the release of inflammatory mediators, initiating an anti-fibrinolytic-coagulation cascade. Circulating platelets activate upon encountering exposed collagen, aggregating to form a fibrin clot for rapid hemostasis. Subsequently, platelets and damaged epithelial and endothelial cells produce various chemotactic factors

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and MMPs, facilitating the efficient recruitment of inflammatory monocytes and neutrophils to the injury site. During the leukocyte migration phase of wound healing, activated macrophages and neutrophils —key components of the innate immune system—phagocytose and clear tissue debris, apoptotic cells, and invading pathogens. Concurrently, they secrete a range of cytokines and chemokines that orchestrate and amplify the local inflammatory response, thereby facilitating subsequent phases of tissue repair. The second phase involves the activation of effector cells. T cells activate and secrete profibrotic cytokines such as interleukin-13 (IL-13) and TGF-β, further activating macrophages and fibroblasts [13]. Activated fibroblasts transform into myofibroblasts expressing α-smooth muscle actin (α-SMA) to facilitate wound closure [14]. Myofibroblasts produce substantial quantities of ECM, particularly Collagen I (Col I) and fibronectin. Epithelial cells may undergo epithelial-mesenchymal transition (EMT), providing a renewable source of myofibroblasts [4-13]. The third phase involves the elaboration of ECM. During repeated injury, myofibroblasts persist at the wound site, contributing to excessive collagen production and ECM accumulation, leading to fibrotic scar formation [4]. Typically, ECM deposition is balanced by collagen synthesis and catabolism, regulated by various MMPs and tissue inhibitors of metalloproteinases (TIMPs) [13]. The second and third phases overlap with the fourth phase, during which dynamic deposition and insufficient resorption of ECM promote progression to fibrosis and ultimately to end-organ failure [9].

Panax species (Araliaceae), particularly *P. ginseng* [15], *P. quinquefolius* [16], *P. notoginseng* [17, 18], and *P. japonicus* [19], have been extensively utilized in traditional medicine due to their notable tonifying properties [20]. *P. ginseng* C. A. Meyer, a renowned herbal medicine in eastern Asia for millennia, has been employed to treat various ailments [21, 22], regulate the immune system, and protect against cardiovascular diseases [15]. *P. notoginseng* is widely used in traditional Chinese medicine for treating traumatic injuries [18, 23], as well as cardiovascular and cerebrovascular disorders [17, 24]. *P. quinquefolium* demonstrates a broad spectrum of therapeutic and pharmacological effects, including neuroprotective, anti-tumor, anti-diabetic, immunomodulatory, and anti-aging properties [25]. *P. japonicus* serves as a unique substitute for ginseng roots [19]. Currently, numerous plant metabolites, including ginsenosides, polysaccharides, flavonoids, organic acids (esters), amino acids, sterols, and carbenes, have been identified in various *Panax* plants. Among these, ginsenosides are considered the primary active components [20], with over 150 ginsenosides identified to date [26]. Ginsenosides are dammarane- or oleanane-type tetracyclic triterpenoid sapogenins linked to sugar moieties [27]. Dammarane-type ginsenosides share a four-ring hydrophobic steroid-like structure and are classified into two functional groups based on their preferred glycosylation sites at the C6 position: protopanaxadiol (PPD), such as ginsenoside Rb1, Rc, Rb2, Rd, Rg3, and Rh2; and protopanaxatriol (PPT), such as ginsenoside Rg1, Re, Rg2, Rf, and Rh1 [28, 29]. Oleanane-type ginsenosides, including ginsenoside Ro, are relatively less abundant [25]. Previous studies have documented the pharmacological properties of both ginseng and ginsenosides in relation to lung diseases [30-32], diabetes mellitus [33], cardiovascular diseases [34, 35], aging, cancer [36, 37], neuro-regulation [24-38], and immunoregulation [23]. Some ginsenosides show potential for development as medicines or dietary supplements, such as ginsenosides Rg3 and Rh2 for neurodegenerative diseases, Re for diabetic retinopathy, and Rg1 for vascular diseases [39]. Recent evidence has elucidated the fibrosis-alleviating effects of ginsenosides. This review summarizes the mechanisms by which ginsenosides exert their therapeutic effects on various fibrotic diseases and discusses their potential benefits as promising natural products for the prevention and treatment of organ fibrosis.

2. Therapeutic effects of ginsenosides in fibrotic diseases

2.1. Liver fibrosis

Liver fibrosis represents a critical indicator in patients with various chronic liver diseases, serving as a predictor for the risk of future liver-related morbidity [40]. Prolonged hepatic inflammation can lead to diffuse hepatic fibrosis, eventually progressing to cirrhosis, where the normal liver architecture is replaced by regenerative nodules, ultimately resulting in liver failure [41]. Hepatic fibrosis stems from diverse liver conditions, including viral, toxic, metabolic, and autoimmune diseases [42]. This section provides an overview of several anti-fibrotic therapeutic strategies and presents examples of ginsenosides that either inhibit hepatic inflammation, suppress myofibroblast activation, proliferation, and ECM deposition in the fibrotic liver, or facilitate fibrosis resolution.

2.2. Attenuating effects of PPD-type ginsenosides

PPD-type ginsenosides have been shown to inhibit the activation of hepatic stellate cells (HSCs) by directly binding to TGF-β receptor 1 (TGFβR1) and blocking the transmission of the TGF-β1 pathway, thus treating fibrosis [43]. Among the PPD-type ginsenosides, Rg3 has received the most attention for its ability to alleviate collagen deposition and induce HSC inactivation and apoptosis. A study by Xu et al. demonstrated that Rg3 mitigated liver necrosis and fibrosis by reducing lobular destruction, apoptosis, collagen deposition, and septal generation in D-Gal-induced aged mice, potentially through the inhibition of TGF-β and α-SMA secretion [44]. Ginsenoside Rg3 significantly attenuated carbon tetrachloride (CCl_4)-induced liver fibrosis, accompanied by collagen downregulation. *In vitro*, Rg3 contributed to HSC inactivation and induced HSC ferroptosis by regulating Acyl-CoA synthetase long-chain family member 4 (ACSL4) methylation through micro ribonucleic acid (miR)-6945-3p-mediated DNA methyltransferase 3 beta inhibition [45]. Liu et al. investigated the hepatic fibrosis-reversing effect of Rg3 in a thioacetamide (TAA)-chronic mice model. Rg3 reduced the expression of autophagy-related proteins in mice and inhibited the survival of activated HSCs. Notably, Rg3 exhibited dose-dependent inhibition of autophagy, characterized by decreased expression of p62 and reduced transformation of microtubule-associated protein 1 light chain 3 alpha into microtubule-associated protein 1 light chain 3 beta in lipopolysaccharide (LPS)-induced HSCs. Moreover, Rg3 enhanced the phosphorylation of phosphatidylinositol 3-kinase (PI3K) and protein kinase B (Akt) both *in vivo* and *in vitro* [46].

Other saponins in the PPD family have been shown to impede liver fibrosis progression by influencing collagen deposition and effector cell apoptosis. Ginsenoside Rh2 has attracted interest for its potential to modulate HSC inactivation and apoptosis in liver fibrosis, possibly through promoting ferroptosis or autophagy. Mechanistically, Rh2 upregulates interferon regulatory factor 1 expression, leading to the downregulation of solute carrier family 7, member 11 (SLC7A11), which is crucial in inducing ferroptosis and inactivating HSCs. Rh2 has also demonstrated efficacy in alleviating liver fibrosis by reducing hepatic inflammation [47]. Ginsenoside Rd has been found to downregulate fibrosis markers in TAA-induced mice livers and suppress ECM in HSCs or primary hepatocytes. Rd attenuates fibrogenesis and inflammation in hepatic fibrosis by regulating the estrogen-related receptor α (ERRα)-P2X7 receptor (P2X7r) signaling pathway mediated NLR family pyrin domain containing 3 (NLRP3) inflammasome activation [48]. Ginsenoside Rc downregulates fibrosis markers in CCl_4-induced mouse livers, including α-SMA, Col I, and the TIMP-1/MMP13 ratio. Additionally, Rc suppresses ECM produc-

tion in HSCs. Mechanistically, Rc reduces inflammatory reactions by regulating the nerve growth factor-induced gene B (Nur77)-toll-like receptor 4 (TLR4) signaling pathway while suppressing fibrogenesis [49]. Ginsenoside Rg5 significantly suppresses fibrotic proteins (α-SMA, Col I, TGF-β) in the liver. Following Rg5 intervention, lipid accumulation, and hepatocyte apoptosis are inhibited *via* the Notch1 signaling pathway in NASH mice [50]. Lin et al. highlighted ginsenoside Rb1's novel role in inducing HSC ferroptosis and promoting HSC inactivation. Specifically, Rb1 reduces α-SMA and Col I levels in HSCs. Rb1 promotes HSC ferroptosis both *in vivo* and *in vitro*, characterized by increased glutathione depletion, malondialdehyde production, iron overload, and reactive oxygen species (ROS) accumulation. The protective effect is partially attributed to its modulation of beclin-1 (BECN1) and SLC7A11. Notably, BECN1 suppression counteracts Rb1's effects on HSC inactivation, and BECN1 can directly interact with SLC7A11, initiating HSC ferroptosis [51].

Recent studies have illuminated the potential of novel ginsenosides in attenuating inflammation and collagen deposition associated with liver fibrosis. Li et al. demonstrated that ginsenoside AD-2 mitigated TAA-induced hepatic fibrosis in mice by suppressing the expression of F4/80 and inflammatory mediators, including IL-1β, IL-1R1, and IL-18. This effect was attributed to the inhibition of the Raf-mitogen-activated protein kinase (MEK) signaling pathway, thereby ameliorating liver fibrosis [52]. Su et al. further reported that AD-2 inhibits ECM deposition and inflammation associated with fibrosis, with its anti-fibrotic effects linked to the modulation of the p-c-Jun N-terminal kinase (JNK) and p38-extracellular regulated protein kinase (ERK) pathways [53]. Moreover, ginsenoside AD-2 has been shown to alleviate LPS-induced activation of HSCs and CCl_4-induced liver damage in mice. The underlying mechanism involves the inhibition of the TGF-β1 pathway and the regulation of TIMP-1/MMP9 through the vitamin D (VD)/VD nuclear receptor (VDR) axis [54]. Ma et al. confirmed that ginsenoside AD-1 inhibited the proliferation of activated HSCs, particularly when combined with selected amino acids, and S-phase arrest is part of the mechanism by which the AD-1 conjugate exerts its anti-proliferative effects [55].

2.3. Attenuating effects of PPT-type ginsenosides

Several studies have documented the effects of PPT-type ginsenosides, particularly Rg1, Rg2, and Rh1, in ameliorating liver fibrosis. Ginsenoside Rg1 has demonstrated the ability to mitigate both aging-induced and LPS-induced liver fibrosis by reducing inflammatory infiltration and collagen deposition. In aging-induced conditions, Rg1's protective effect is associated with the reduction of nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase 4 (NOX4)-mediated ROS oxidative stress and inactivation of the NLRP3 inflammasome [56]. In LPS-induced chronic liver damage, Rg1 potentially acts through the nuclear factor E2 related factor (Nrf2)/Kelch-like ECH-associated protein 1 (Keap1) pathway to inhibit NLRP3, NLRP1, and absent in melanoma 2 (AIM2) inflammasomes in liver cells [57]. Zhang et al. concluded that Rg1 significantly reduces collagenation and HSC reproduction, with evidence of EMT inactivation through the epigenetic modulation of Smad7 expression *via* microRNA-152 [58]. Mo et al. confirmed Rg1's inhibitory effect on HSC proliferation and its attenuation of hepatocyte apoptosis in fibrotic mice, suggesting that Rg1's anti-fibrotic properties are mediated through the alleviation of indoleamine 2,3-dioxygenase 1 (IDO1)-mediated inhibition of dendritic cell maturation [59]. Ginsenoside Rg2 has also shown efficacy in improving liver fibrosis, as reported by Hsu et al., who observed that Rg2 enhances antioxidant activity, reduces lipid accumulation, and alleviates pathological fibrosis [60]. Furthermore, Rg2 ameliorates CDAHFD-induced hepatic fibrosis by restoring impaired autophagy flux and inhibiting TGF-β1 expression through p62 degradation in hepatocytes while reversing LPS-induced HSC activation *via* the Akt/mammalian target of rapamycin (mTOR)-mediated autophagy pathway [61]. Wang et al. found that treatments with Rh1 and Rg2 exert anti-fibrotic effects in non-alcoholic fatty liver disease (NAFLD) mice, with the saponin extract enriched in these ginsenosides mitigating LPS-induced NLRP3 inflammasome activation by promoting mitophagy [62]. Additionally, Re has been reported to downregulate collagen deposition and aminotransferase levels in db/db mice, inhibiting oxidative stress and upregulating peroxisome proliferator-activated receptor γ (PPARγ) expression [63] (Fig. 1).

2.4. Cardiac fibrosis

Permanent fibrosis and chronic deterioration of heart function, resulting from ischemia, ischemia/reperfusion, inflammation, and toxic injury, present a significant global healthcare challenge [64, 65]. MI causes acute necrosis of cardiomyocytes in the affected area, leading to the formation of a reparative fibrotic scar that initially prevents ventricular wall rupture. However, in prolonged HF, interstitial fibrosis accumulates throughout the heart, causing wall and septal stiffening and progressively impairing cardiac function [66]. Cardiac fibrosis, characterized by progressive accumulation of fibrotic tissue, is frequently associated with the pathogenesis of cardiovascular diseases, ultimately leading to HF [67]. Consequently, the development of novel therapies for effective and targeted reversal of myocardial fibrosis in patients remains a primary research focus [68]. Recent studies have demonstrated the potential alleviating effects of various ginsenosides on cardiac function and myocardial fibrosis induced by different stimuli.

2.5. Attenuating effects of PPD-type ginsenosides

PPD-type ginsenosides, particularly Rg3, have demonstrated significant therapeutic effects on myocardial fibrosis, primarily through the classical TGF-β1-Smads pathway. Xu et al. reported that ginsenoside Rg3 improves cardiac function by inhibiting TGFβR1-Smads signaling activation and reducing collagen production, thereby addressing myocardial fibrosis and hypertrophy [69]. Lai et al. confirmed these findings, showing that Rg3 enhances cardiac function, pathological features, and myocardial fibrosis. They identified aminoacylase 1 and FoxO3a as potential Rg3 targets, whose modulation inhibits the TGF-β1-Smads pathway, leading to anti-fibrotic effects [70, 71]. Additionally, Rg3 has been found to mitigate myocardial hypertrophy and fibrosis in both the TAC rat model and Ang II-induced cardiomyocytes. This is achieved by significantly inhibiting the NLRP3-caspase 1 inflammasome and oxidative stress, mechanisms involving the attenuation of nuclear factor-kappa B (NF-κB) activation and the promotion of sirtuin 1 (SIRT1) expression [72].

Ginsenoside Rb1 has been extensively investigated for its capacity to mitigate myocardial fibrosis through various mechanisms, including the regulation of inflammation, metabolic pathways, oxidative stress, and apoptosis. Ke et al. demonstrated that ginsenoside Rb1 treatment in aged hearts reduced collagen deposition by inhibiting the NF-κB signaling pathway, thereby attenuating the inflammatory response associated with aging [73]. Li et al. reported that ginsenoside Rb1 significantly enhanced cardiac structure and metabolism, restored cardiac function, and inhibited both cardiac hypertrophy and fibrosis. The mechanism involves Rb1's direct binding to the Fas-associated death domain, which counteracts its negative impact on PPARα transcription, thus ameliorating cardiac energy imbalance and HF [74]. Jiang et al. demonstrated that ginsenoside Rb1 decreased mitochondrial ROS production, reduced MI size, preserved cardiac function, and limited cardiac fibrosis in a mouse model of left anterior descending

coronary artery occlusion. The proposed underlying mechanism is the inhibition of mitochondrial complex I-mediated ROS burst [75]. Furthermore, ginsenoside Rb1 has been found to attenuate doxorubicin-induced cardiac dysfunction, myocardial hypertrophy, and interstitial fibrosis by suppressing autophagy and ferroptosis, suggesting its potential in preventing these forms of cell death in the heart [76].

Other PPD-type ginsenosides demonstrate potential in addressing myocardial fibrosis through mechanisms currently under clinical investigation, including metabolic pathways, inflammatory signaling, and oxidative stress. Zhang et al. demonstrated that ginsenoside Rb3, in addition to Rb1, directly influences myocardial energy metabolism remodeling and PPARα regulation, thereby ameliorating myocardial fibrosis [77]. Ginsenoside Rd significantly improved myocardial function, attenuated cardiac fibrosis, and inhibited inflammation and apoptosis in myocardial tissues post-infarction. The proposed mechanism involves activation of the Akt/mTOR pathway, regulating macrophage polarization from M1 to M2 type [78]. Following macrophage transformation to M1 state, T cell subsets, including cluster of differentiation 4 $(CD4)^+$, $CD8^+$, and regulatory T cells, emerge as mediators of inflammatory responses, activating the JNK/activator protein 1 (AP-1) signaling pathway. Ginsenosides Rh2 and Rg5 suppressed myocardial fibrosis, hypertrophy, and inflammation in Ang II-challenged mice by inhibiting the JNK/AP-1 pathway, thus preventing cardiac disruption [79, 80]. Rh2 mitigates doxorubicin-induced cardiotoxicity by reducing fibroblast to myofibroblast transition and EMT, promoting myofibroblast senescence, and reversing EMT-induced differentiation [81]. Ginsenoside F2 alleviates isoproterenol (ISO)-induced myocardial fibrosis and enhances antioxidant enzyme activity, including catalase, glutathione, and superoxide dismutase, by modulating expression levels of Keap1, NADPH quinone dehydrogenase 1, Nrf2, and heme oxygenase 1 [82]. The novel ginsenoside AD-2 prevents Ang II-induced hyper-hemodynamics and fibrotic collagen deposition by activating AMP-activated protein kinase (AMPK) signaling in rat atria [83].

2.6. Attenuating effects of PPT-type ginsenosides

PPT-type ginsenosides have demonstrated potential in reducing myocardial fibrosis and improving cardiac function through various mechanisms, as evidenced by preclinical studies. PPT has shown the ability to disrupt the Keap1-Nrf2 interaction, a crucial regulatory axis in oxidative stress response, thereby inhibiting fibroblast activation and proliferation [84]. Among these, Rg1 has emerged as a prominent candidate due to its potential to mitigate myocardial fibrosis. Zhen et al. have elucidated that Rg1-induced mesenchymal stem cells secrete exosomal circNotch1, which activates the Notch signaling pathway and induces macrophage M2 polarization, offering a novel approach to alleviate diabetic cardiomyopathy [85]. Guan et al. have demonstrated that Rg1 significantly improves cardiac remodeling post-MI in mice by attenuating left ventricular dilation and fibrosis and by promoting mitophagy through the SIRT1/PTEN induced kinase 1 (PINK1)/Parkin pathway in H_2O_2-treated H9c2 cells [86]. Lu et al. focused on the attenuation of Rg1 in the abdominal aortic constriction-in-

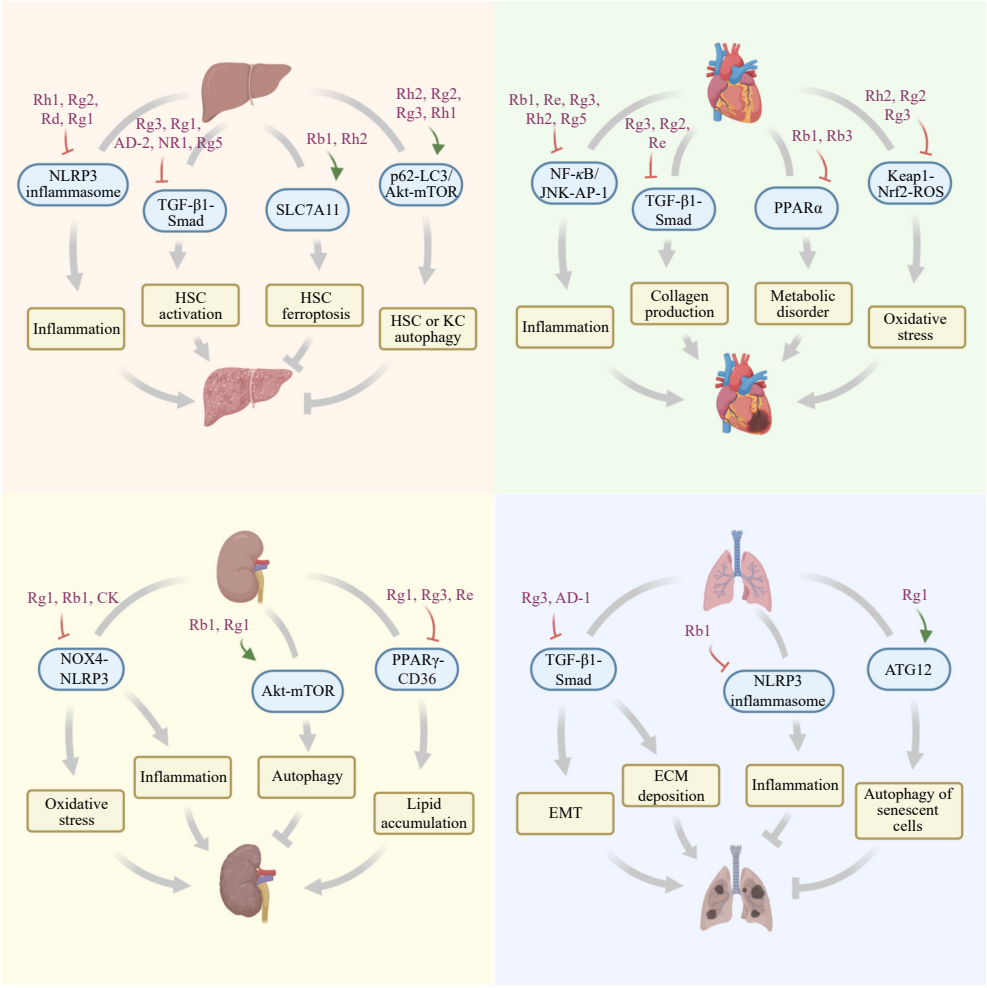

Fig. 1 Summary of the main targets of ginsenosides exerting their anti-fibrotic effects on the` liver, heart, kidney, and lung. In the liver, heart, kidney, and lung, ginsenosides such as Rg1, Rb1, Rh1, Rd, Rg2, Rg3, Rh2, Re, AD-1, AD-2, NR1, Rg5, and CK, etc. affect various stages of the fibrotic process by acting on multiple signaling pathways, thereby slowing down the progression of organ fibrosis.

duced mechanical stress model. They found that Rg1 alleviated cardiac hypertrophy and fibrosis and improved cardiac decompensation *via* the inhibition of CaN pathway and the decrease of Ca^{2+} mediated by calcium-sensing receptors [87]. Wang and colleagues concluded that ginsenoside Rg2 alleviated myocardial fibrosis and improved cardiac function compared to the ISO group, accompanied by suppressed TGF-β1-Smad signaling in heart tissues [88]. Similarly, Li et al. Rg2 induces phosphorylation of Akt, which contributes to improved cardiac function and reduced collagen deposition in mice following MI, as evidenced by a decrease in the expression of fibrosis-associated genes [89]. Ginsenoside Re has been shown to reduce interstitial fibrosis in the left ventricle of MI rats by activating the PI3K/Akt signaling pathway, downregulating TGF-β1 expression, and inhibiting Smad2/3 activation [90]. Additionally, Sun et al. found that Re enhances cardiac function and suppresses collagen deposition in an acute MI model through modulation of the miR-489/myd88/NF-κB signaling axis [91]. Lastly, the research by Wang et al. suggests that ginsenoside Rh4 can inhibit myocardial hypertrophy, inflammation, and oxidative stress induced by Ang II, with nuclear factor IL-3 serving as a downstream regulator, indicating its potential for cardiovascular protection [92] (Fig. 1).

2.7. Renal fibrosis

Renal fibrosis represents a prevalent histological indicator of functional deterioration in the kidney. Without effective intervention, it can progress to end-stage renal disease, a condition manageable only through dialysis or transplantation and associated with a mortality rate at least three times higher than that of the general population. Fibrosis emerges as a reactive process in response to various factors, including unilateral ureteral obstruction (UUO), diabetic nephropathy, or drug toxicity. This process initiates excessive epithelial injury and inflammation, subsequently leading to myofibroblast activation and accumulation of ECM [93]. Several studies have indicated that ginsenosides may exhibit inhibitory or even reversal effects on renal fibrosis.

2.8. Attenuating effects of PPD-type ginsenosides

Additionally, PPD-ginsenosides demonstrate therapeutic efficacy in mitigating renal fibrosis. Administration of CK ameliorated renal tubulointerstitial lesions, as evidenced by reduced urinary proinflammatory cytokine levels and attenuated mononuclear leukocyte infiltration and fibrosis. These beneficial effects correlated with the inhibition of the NLRP3 inflammasome and the TGF-β1-dependent Smad2/3 fibrotic pathway [94]. Ni et al. identified Rb1 as a potent inhibitor of ROS generation and subsequent activation of Bip/eIF2α/CHOP signaling, thereby preventing bavachin-induced ER stress and subsequent EMT and renal fibrosis [95]. Furthermore, Liu et al. demonstrated that Rb1 modulates renal dysfunction by inhibiting UUO-induced autophagy. This effect is mediated through the AMPK/mTOR and ERK/p38 MAPK signaling pathways [96]. Sui et al. concluded that Ginsenoside Rg3 exhibited comparable efficacy to ginsenoside Re in preventing diabetic kidney disease in db/db mice, upregulating PPARγ expression, and downregulating inflammatory and fibrotic biomarkers [97]. Ginsenoside Rh2 significantly attenuated renal fibrosis and renal cell apoptosis in diabetic nephropathy models by downregulating discoid domain receptor 1 [98], demonstrating potential in alleviating renal injury and improving renal function [98, 99].

2.9. Attenuating effects of PPT-type ginsenosides

A growing body of research indicates that ginsenoside Rg1 exhibits protective effects against renal injury by mitigating oxidative stress and inflammation, potentially benefiting various chronic kidney diseases [100, 101]. Accumulating evidence demonstrates that ginsenoside Rg1 ameliorates renal fibrosis induced by multiple factors, primarily through the inactivation of NOX4. Shen et al. observed that Rg1 significantly alleviated glomerular mesangial proliferation and downregulated elevated Col IV levels in aged mice. Furthermore, Rg1 treatment substantially reduced ROS generation and NOX4 expression in the renal cortex, as well as the expression of NLRP3 inflammasome-related proteins and IL-1β. These findings suggest that Rg1 inhibits aging-related glomerular fibrosis by reducing NOX4-derived ROS generation and downregulating NLRP3 inflammasome expression [102]. Zhang et al. reported that Rg1 also attenuates LPS-induced chronic renal injury, improves renal function impairment, and mitigates renal fibrosis. The mechanisms may involve reducing NOX4-mediated oxidative stress and inhibiting NLRP1 inflammasome [101]. Ji et al. demonstrated that Rg1 significantly improved lipid deposition, fibrosis, and ROS production in type 2 diabetes mellitus (T2DM) mice kidneys *via* inhibition of NOX4-MAPK signaling [103]. Beyond NOX4, ginsenosides can also influence ROS production in the kidney through other targets and pathways, such as aldose reductase, the Nrf2-HO-1 pathway, and mitophagy [104-106]. Moreover, in streptozotocin (STZ)-induced diabetic rats, ginsenoside Rg1 alleviated renal fibrosis and podocyte EMT by enhancing Akt/glycogen synthase kinase 3β (GSK3β)/β-catenin pathway-mediated autophagy, indicating its therapeutic potential for DN and other glomerular diseases [107]. Eight weeks of Rg1 treatment was found to significantly attenuate glomerular fibrosis and reduce blood lipid levels and renal lipid accumulation in T2DM mice. The mechanism may involve reducing CD36 overexpression and inhibiting the transient receptor potential cation channel subfamily C member 6 (TRPC6)/nuclear factor of activated T cells 1 (NFAT2) signaling pathway in renal tissues [100]. Additionally, another PPT-type ginsenoside, ginsenoside Re, improved renal fibrosis through the regulation of autophagy in murine models with UUO or aristolochic acid nephropathy (AAN) [108] (Fig. 1).

2.10. Pulmonary fibrosis

Fibrotic lung disease encompasses a diverse group of pulmonary disorders characterized by progressive nature and associated with significant morbidity and premature mortality [109, 110]. The pathogenesis and progression of idiopathic pulmonary fibrosis are linked to the inhalation of various particulates, including tobacco smoke, metal and wood dust, agricultural particles, viral agents, and stone and silica particles [111]. Despite the severity of these conditions, early-stage therapeutic interventions for pulmonary fibrosis remain limited. Recent research has identified ginsenosides as promising candidates for the treatment of fibrotic lung disease.

2.11. Attenuating effects of total ginsenosides

Research indicates that total ginsenosides likely play a mitigating role in pulmonary fibrosis. Liu et al. formulated a solution of total saponins from *Panax notoginseng*, comprising notoginsenoside R1, ginsenoside Rg1, Re, Rb1, and Rd. Their *in vivo* evaluation demonstrated a protective effect against bleomycin (BLM)-induced idiopathic pulmonary fibrosis [112]. Additionally, El-Bassouny et al. elucidated the role of ginsenosides in significantly improving lung structure and reducing NF-κB expression in BLM-induced rats [113].

2.12. Attenuating effects of PPD-type ginsenosides

Multiple studies have confirmed the ameliorating effect of PPD-ginsenosides on pulmonary fibrosis, primarily through the

suppression of the TGF-β1 signaling pathway. Li et al. demonstrated that AD-1 mitigated injury, ECM accumulation, and α-SMA protein levels in BLM-induced pulmonary fibrosis, potentially through modulation of the TGF-β1/TIMP-1/α-SMA signaling pathway [114]. Yun et al. reported that ginsenoside Rg3 administration reduced EMT and inhibited BLM-induced pulmonary fibrosis progression, characterized by attenuation of spindle-shaped morphology and EMT marker expression. They elucidated the mechanism by which Rg3 inhibited EMT through regulation of the Smad2/3 signaling pathway [115]. Fu et al. found that Rg3 improved BLM-induced pulmonary fibrosis by binding to HIF-1α and inhibiting its nuclear localization, subsequently inactivating the HIF-1α/TGF-β1 signaling pathway and further preventing fibroblast migration and proliferation through EMT [116]. Ginsenoside Rb1 ameliorated BLM-induced pulmonary inflammation and fibrosis by suppressing NLRP3 inflammasome activation and the NF-κB pathway. *In vivo* studies revealed that Rb1 inhibited LPS- and ATP-induced NLRP3 inflammasome activation in macrophages [117]. Research by Ren et al. discovered that treatment with ginseng saponin metabolite 20(S)-PPD alleviated BLM-induced pulmonary fibrosis by modulating the AMPK/stimulator of interferon response CGAMP interactor 1 (STING) signaling pathway, thereby reducing the expression of fibrotic hallmarks [118].

2.13. Attenuating effects of PPT-type ginsenosides

Ginsenoside Rg1, derived from PPT-ginsenosides, demonstrates potential therapeutic effects on pulmonary fibrosis. Ma et al. elucidated that Rg1 attenuates lung fibrosis and injury in mice with T2DM-associated pulmonary tuberculosis by inhibiting the signal transducer and activator of transcription 3 (STAT3) expression through miR-15b-5p [119]. Additionally, Huang et al. reported that Rg1 treatment could mitigate paraquat-induced pulmonary fibrosis and reduce senescence by enhancing autophagy activity in an autophagy-related gene 12 (ATG12)-dependent manner [120] (Fig. 1).

2.14. Miscellaneous diseases

Ginsenosides demonstrate potential attenuating effects in organic fibrosis caused by various diseases beyond those previously mentioned. Song et al. reported that ginsenoside Rg1 alleviated endometrial fibrosis in a mouse model of LPS-induced endometritis by inhibiting the ROS/NLRP3 inflammasome signaling pathway, as evidenced by the suppression of EMT in bovine endometrial epithelial cells [121]. Additionally, Rg1 treatment ameliorated glucose and lipid metabolism disorders and pancreatic fibrosis in STZ-induced T1DM mice, with mechanisms involving AMPK activation and inhibition of mTOR-mediated autophagy [122]. Furthermore, Cho and colleagues elucidated the potential role of ginseng aqueous extract (containing 30 $\mu g \cdot mL^{-1}$ of ginsenosides) in cystic fibrosis chronic rhinosinusitis by stimulating Cl^- secretion, thereby augmenting airway surface liquid depth and ciliary beat frequency [123].

3. Conclusions and perspectives

3.1. Summary of the anti-fibrotic mechanisms and pathways of ginsenosides

Fibrosis is characterized by the pathological accumulation of ECM, primarily composed of collagen and fibronectin, leading to tissue and organ dysfunction, potentially resulting in organ failure and mortality. Recent research has revealed novel therapeutic possibilities for fibrotic diseases, particularly within the domain of Chinese herbal medicine and its active constituents. *Panax ginseng* C. A. Meyer, a globally recognized medicinal herb, is renowned for its immunomodulatory properties and efficacy against various ailments. Ginsenosides, the primary active components in ginseng, are also the key constituents responsible for the biological functions of the *Panax* genus in traditional Chinese medicine. Notably, ginsenosides have emerged as the principal bioactive compounds with potential for treating fibrotic conditions [20].

This review integrates the mechanisms by which ginsenosides mitigate various forms of organ fibrosis (Table 1), detailing the key stages of fibrosis development and the therapeutic impact of ginsenosides at each stage. Ginsenosides have demonstrated the ability to reduce fibrosis through several key actions: (i) mitigating parenchymal cell injury and the subsequent inflammatory response by inhibiting the NF-κB/JNK-AP-1 pathway or reducing NLRP3 inflammasome formation, (ii) preventing the activation of myofibroblasts derived from diverse precursor cells by suppressing the TGFβ1-Smad signaling pathway, (iii) inhibiting myofibroblast proliferation and ECM secretion *via* the TGFβ1-Smad pathway, and (iv) promoting the apoptosis or inactivation of myofibroblasts through autophagy or ferroptosis, mediated by the p62-LC3/Akt-mTOR/ATG12/SLC7A11 signaling cascade (Fig. 2). In the initial phase of inflammatory response activation, ginsenosides AD-2, Rh1 and Rg2, Rd, Rg1, Rc, Rb1, Re, Rg3, F2, CK and notoginsenoside R1 primarily exert their effects by reducing NOX4-mediated ROS oxidative stress, inhibiting NLRP3 inflammasome activation, and downregulating cytokine levels in various fibrotic models. During ECM deposition, ginsenosides AD-1, AD-2, Rg2, Rg1, Rb1, Re, Rg3, CK, and notoginsenoside R1 reduce collagen deposition, potentially through inhibition of TGFβ1 and α-SMA secretion and suppression of activated myofibroblast proliferation. In terms of ECM resolution, ginsenosides Rb1, Rg3, Rh2, Rg2, Rg1, and Re induce myofibroblast inactivation, ferroptosis, and autophagy. For instance, ginsenosides inactivate HSCs through inhibition of TGFβ1-Smad signaling, initiate HSC ferroptosis *via* the key regulator SLC7A11, and induce myofibroblast autophagy through Akt-mTOR or p62-LC3 pathways. The antifibrosis effects of ginsenosides have been observed across multiple human organs, with hepatic and cardiac fibrosis demonstrating the most advanced research and clearest mechanisms.

Over the past five years, research has demonstrated the antifibrotic effects of PPD ginsenosides, including Rb1, Rb3, Rc, Rd, Rg3, Rh2, F2, AD-1, and AD-2. Among these, ginsenoside Rg3 has garnered the most attention for its anti-fibrotic properties. Rg3 exhibits broad intervention in fibrotic diseases affecting the liver, heart, kidney, and lung, showing improvement at various stages of the pathological process. Specifically, Rg3 significantly inhibits inflammatory responses, EMT, and collagen deposition while promoting apoptosis or inactivation of activated myofibroblasts. These effects are mediated through the regulation of NF-κB, TGFβR1-Smads, ferroptosis, and autophagy-related signaling pathways [44-46, 69-72, 115-116]. Recent studies have also elucidated the anti-fibrotic effects of PPT ginsenosides Re, Rh1, Rg1, and Rg2, with Rg1 receiving particular attention. Similar to Rg3, Rg1 demonstrates a wide range of influence on fibrotic diseases, including those affecting the liver, heart, kidney, and lung, as well as endometrial and pancreatic fibrosis. Specifically, Rg1 reduces ROS oxidative stress, inflammatory cell infiltration, collagen deposition, EMT, macrophage M2 polarization, and lipid metabolism disorder. It also enhances autophagy activity by targeting NLRP3 inflammasome activation, Keap1-Nrf2 signaling, Smad7 expression, Akt/GSK3β/β-catenin pathway, STAT3 expression, TRPC6/NFAT2 signaling, AMPK/mTOR signaling, and ATG12-dependent mechanisms [56-58, 100-107, 119-120, 122]. Notably, novel ginsenosides such as AD-1 and AD-2 show potential in attenuating fibrosis. AD-1 inhibits cell proliferation of activated HSCs by inducing S-phase arrest [55]and reduces ECM buildup in pulmonary fibrosis by silencing the TGF-β1/TIMP-1/α-SMA signaling path-

Table 1 The processes and pathways of ginsenosides to reverse fibrosis-associated diseases.

Ginsenosides	Fibrosis organ	Model (*In vivo*)	Model (*In vitro*)	Effects	Mechanisms	Refs
AD-1	Liver	-	Activated t-HSC/Cl-6 cells	Inhibited cell proliferation and activated apoptosis	The induction of S-phase arrest	55
AD-1	Lung	Bleomycin-induced pulmonary fibrosis in mice	LPS-induced fibroblast injury in L929 cells	Reduced ECM deposition	The inhibition of TGF-β1/TIMP1/α-SMA pathway	114
AD-2	Heart	Ang II induced heart injury in rat	-	Reduced ECM deposition	The activation of AMPK	83
AD-2	Liver	CCl_4-induced liver fibrosis in mice	LPS-induced t-HSC/Cl-6 cell activation	Reduced pathological changes and enhanced liver function; Inhibited HSC activation	The inhibition of TGF-β1 pathway and regulation of TIMP1/MMP9	54
AD-2	Liver	TAA-induced liver injury in mice	-	Reduced lipid accumulation, inflammatory response and apoptosis; Reduced ECM deposition	The inhibition of Raf–MEK pathway; The inhibition of p-JNK and p38-ERK pathways	52, 53
Compound K	Kidney	UUO-induced renal fibrosis in mice	MICP-induced TECs	Reduced inflammation	The inhibition of NLRP3 inflammasome and TGF-β1-Smad2/3 pathway	94
F2	Heart	ISO-induced myocardial infarction in rat	ISO-induced H9c2 cells	Reduced cardiocyte apoptosis, oxidative stress, and mitochondrial dysfunction	The activation of Keap1-Nrf2 and PI3K-Akt pathways	82
PPD	Liver	-	TGF-β1-activated LX-2	Inhibited the activation of HSC	The inhibition of TGF-β1 pathway	43
PPT	Heart	LAD-induced myocardial infarction in rat	Ang II-induced fibroblast activation	Improved cardiac function and ameliorated cardiac fibrosis in MI rats; Reduced Ang II-induced fibroblast differentiation and proliferation, suppressed oxidative stress	The activation of Keap1-Nrf2 pathway	84
Rb1	Liver	CCl_4-induced liver fibrosis in mice	CCl_4-activated primary HSCs and LX-2 cells	Promoted HSC ferroptosis both in vivo and in vitro	The activation of BECN1-SLC7A11 pathway	51
Rb1	Heart	Aged mice	-	Reduced ECM deposition and inflammatory response	The inhibition of NF-κB pathway	73
Rb1	Heart	Doxorubicin induced acute cardiotoxicity in mice	-	Suppressed autophagy and ferroptosis	-	76
Rb1	Heart	ISO-induced heart failure in rat	ISO-stimulated NRCM	Ameliorated cardiac energy derangement	The activation of PPARα pathway via inhibiting FADD	74
Rb1	Heart	I/R-induced myocardial infarction in rat	H/R-stimulated NRCM	Decreased mitochondrial ROS production	The inhibition of mitochondrial complex I-mediated ROS burst	75
Rb1	Kidney	Bavachin-induced renal fibrosis in zebrafish	Bavachin-stimulated HK-2 cells	Ameliorated EMT in bavachin-induced zebrafish; Downregulated ER stress by inhibiting ROS generation in HK-2 cells	The inhibition of Bip-eIF2α-CHOP pathway	95
Rb1	Kidney	UUO-induced renal fibrosis in mice	HBSS-induced HK-2 cells	Restrained activation of autophagy	The regulation of AMPK-mTOR pathway	96
Rb1	Lung	Bleomycin-induced pulmonary fibrosis in mice	-	Reduced pulmonary inflammation and disturbed the crosstalk between macrophages and fibroblasts	The inhibition of NLRP3 inflammasome activation and the NF-κB pathway.	117
Rb3	Heart	TAC-induced myocardial fibrosis in rat	Ang II-induced cardiac fibroblasts	Improved myocardial energy metabolism	The activation of PPARα pathway	77
Rc	Liver	CCl_4-induced liver fibrosis in mice	TGF-β1-induced t-HSC/Cl-6 cells	Reduced inflammatory reaction and suppressed the production of ECM	The inhibition of Nur77-TLR4/MyD88 signaling pathway	49
Rd	Liver	TAA-induced hepatic fibrosis in mice	TGF-β1-induced t-HSC/Cl-6 cells and primary hepatocyte	Reversed inflammatory response and suppressed the ECM	The inhibition of ERRα-P2X7r-mediated NLRP3 inflammasome	48
Rd	Heart	LAD-induced myocardial infarction in mice	-	Reduced inflammation and apoptosis	The activation of AKT/mTOR pathway to enhance the transformation of Ly6C-high Monocytes/Macrophages to Ly6C-low Monocytes/Macrophages	78
Re	Liver	db/db mice	-	Reduced collagen deposition, inflammation and oxidative stress	The upregulation of PPARγ expression	63
Re	Heart	AMI model mice	Ang II-induced cardiac fibroblasts	Reduced collagen deposition and fibroblast migration	The inhibition of miR-489/myd88/NF-κB pathway	91
Re	Heart	LAD-induced myocardial infarction in rat	-	Reduced oxidative stress and interstitial fibrosis	The inhibition of AMPK-TGF-β1-Smad2/3 and activation of FAK-PI3K-Akt pathways	90
Re	Kidney	UUO or aristolochic acid-induced nephropathy in mice	TGF-β1-induced HK-2	Reduced autophagy	-	108
Rg1	Liver	SAMP8 mice	-	Reduced oxidative stress and inflammation	The inhibition of NOX4-NLRP3 inflammasome activation	56
Rg1	Liver	LPS-induced chronic liver damage model in mice	LPS-induced HepG2 cells	Reduced inflammation	The activation of Keap1-Nrf2 pathway and further inhibition of NLRP3, NLRP1, and AIM2 inflammasomes	57
Rg1	Liver	CCl_4-induced liver fibrosis in mice	CCl_4-induced primary HSC or t-HSC/Cl-6 cells	Reduced collagen deposition, HSC reproduction and EMT; Reduced HSC proliferation and attenuated hepatocyte apoptosis	The induction of Smad7 expression via microRNA-152; The alleviation of IDO1-mediated the inhibition of DCs maturation	58, 59
Rg1	Heart	Abdominal aortic constriction-induced mechanical stress in rat	Mechanical stretching-induced cardiomyocytes and cardiac fibroblasts	Improved cardiac decompensation	The activation of CaN pathway and the increase of Ca^{2+} mediated by calcium sensing receptor	87

Continued

Ginsenosides	Fibrosis organ	Model (*In vivo*)	Model (*In vitro*)	Effects	Mechanisms	Refs
Rg1	Heart	LAD-induced myocardial infarction in mice	H_2O_2-treated H9c2	Attenuated apoptosis and fibrotic responses	The activation of SIRT1-PINK1-Parkin axis	86
Rg1	Heart	Diabetic cardiomyopathy mice	HG-induced primary cardiac fibroblasts	Induced macrophage M2 polarization	The secretion of exosomal circNotch1 activating the Notch1 pathway	85
Rg1	Kidney	STZ-induced diabetic rats	High glucose-treated podocytes	Reduced podocyte EMT	The activation of Akt/GSK3β/β-catenin pathway-mediated autophagy	107
Rg1	Kidney	SAMP8 mice	-	Alleviated glomerular mesangial proliferation and decreased levels of fibrotic markers	The inhibition of NOX4-derived ROS generation and downregulating NLRP3 inflammasome expression	102
Rg1	Kidney	HFD + STZ induced T2DM in mice	-	Attenuated renal pathological injury, renal lipid accumulation and glomerular fibrosis	The inhibition of CD36-TRPC6-NFAT2 pathway	100
Rg1	Kidney	LPS-induced chronic renal injury in mice	-	Decreased the levels of fibrosis markers and reduced oxidative stress	The inhibition of NOX4-NLRP3 pathway	101
Rg1	Kidney	HFD-induced T2DM in mice	PA and PA + HG exposure in human mesangial cells	Improved lipid deposition and ROS production	The inhibition of NOX4-MAPK pathway	103
Rg1	Lung	T2DM-associated pulmonary tuberculosis in mice	-	Reduced inflammation	The inhibition of STAT3 expression by miR-15b-5p	119
Rg1	Lung	Paraquat-induced epithelial cell senescence in mice	Paraquat-induced senescence in epithelial cells	Decreased senescence, enhanced autophagy activity and senescence associated secretory phenotype expression	The induction of the expression of ATG12	120
Rg2	Liver	CDAHFD-induced liver fibrosis in mice	Oleic acid-stimulated hepatocytes; LPS-induced t-HSC/Cl-6 cells	Decreased the levels of fibrosis markers and autophagy-related proteins in mice; Restored the autophagy impairment in hepatocytes and HSC	The activation of AKT-mTOR pathway	61
Rg2	Liver	CCl_4-induced liver fibrosis in mice	-	Improved antioxidant activity and decreased lipid accumulation	-	60
Rg2	Heart	ISO-induced heart failure in mice	-	Alleviated myocardial fibrosis and improved cardiac function	The inhibition of TGF-β1-Smad pathway	88
Rg2	Heart	AMI model mice	Ang II-induced cardiac fibroblasts	Improved cardiac function and inhibited collagen deposition	The activation of Akt pathway	89
Rg3	Liver	D-Gal-induced aged mice	-	Inhibited secretion of fibrosis-related proteins	-	44
Rg3	Liver	CCl_4-induced liver fibrosis in mice	Activated primary HSC	Decreased collagen production, induced HSC inactivation and ferroptosis	The inhibition of ACSL4 methylation by miR-6945-3p-mediated DNMT3B inhibition	45
Rg3	Liver	TAA-induced subacute and chronic hepatic injury in mice	LPS-induced rat t-HSC/Cl-6 cells	Decreased deposition of collagen fibers, reduced expression of fibrosis-related proteins and autophagy-related proteins in mice; Inhibited the survival of activated HSC	The activation of PI3K/Akt-mTOR pathway	46
Rg3	Heart	LAD-induced MI in mice	TGF-β1-stimulated cardiac fibroblasts	Ameliorated collagen production, myocardial fibrosis and hypertrophy as well as enhanced cardiac function	The inhibition of TGF-β1-Smads pathway	69
Rg3	Heart	Coronary artery ligation in mice	Ang II-induced mouse cardiac fibroblasts	Improved cardiac function and pathological features, attenuated myocardial fibrosis	The induction of ACY1 expression and inhibition of TGF-β1-Smad3 pathway	70
Rg3	Heart	TAC-induced myocardial fibrosis in rat	Ang II-stimulated human cardiomyocyte cell line AC16 and HCM	Reduced inflammation and oxidative stress	The inactivation of NLRP3 inflammasome by modulating the SIRT1/NF-κB pathway	72
Rg3	Heart	Ischemia-reperfusion model in rat	H/R-induced H9c2 cells	Inhibited the promotion of oxidative stress, inflammation, and fibrosis	The inhibition of FoxO3a-TGF-β-Smad pathway and NF-κB activation	71
Rg3	Lung	Bleomycin-induced pulmonary fibrosis in mice	HPAECs induced by co-treatment with TGF-β2 and IL-1β	Alleviated the characteristics of EMT such as spindle-shaped morphological, EMT marker expression, Dil-Ac-LDL uptake and migratory properties	The inhibition of Smad2/3 pathway	115
Rg3	Lung	Bleomycin-induced pulmonary fibrosis in mice	Bleomycin-stimulated LL 29 cells	Inhibited the migration and proliferation of fibroblasts through EMT	The inhibition of the nuclear localisation of HIF-1α and the following TGF-β1 pathway	116
Rg3	Kidney	db/db mice	-	Upregulated the expression of PPARγ and downregulated the biomarkers of inflammation and fibrosis	-	97
Rg5	Liver	HFHC + CCl_4-induced NASH model in mice	Activated LX-2 cells	Reduced fibrotic proteins	The inhibition of Notch1 pathway	50
Rg5	Heart	Ang II-induced cardiac inflammation in mice	Ang II-induced cardiomyocytes	Inhibited cardiac inflammation, myocardial fibrosis, and hypertrophy, and prevented cardiac malfunction	The inhibition of JNK/AP-1 pathway	80
Rh1 and Rg2	Liver	Fast food diet-induced hepatic fibrosis in mice	Activated primary HSC, PA-induced primary hepatocytes and LPS-induced Kupffer cells	Alleviated hepatic steatosis, fibrosis, and inflammation in mice; Showed anti- Anti-steatotic effects in primary hepatocytes, anti-fibrosis in hepatic stellate cells, and anti-inflammatory plus pro-mitophagy actions in Kupffer cells	The inhibition of NLRP3 inflammasome activation	62
Rh2	Liver	CCl_4-induced liver fibrosis in mice	Activated primary HSC	Enhanced HSC ferroptosis to reduce HSC proliferation and activation, inhibited liver inflammation	The inhibition of SLC7A11 expression	47

Continued

Ginsenosides	Fibrosis organ	Model (*In vivo*)	Model (*In vitro*)	Effects	Mechanisms	Refs
Rh2	Heart	Ang II-induced hypertensive heart failure in mice	Ang II-induced NRVMs and cardiac fibroblasts	Reduced inflammation	The inhibition of JNK/AP-1 pathway	79
Rh2	Heart	-	Doxorubicin-induced cardiotoxicity in human cardiac ventricle fibroblasts and HUVEC	Reduced fibroblast to myofibroblast transition and EMT, promoted senescence in myofibroblasts and reversed myofibroblast differentiation in EMT	-	81
Rh2	Kidney	STZ-induced diabetic nephropathy in rat	-	Reduced apoptosis and decreased expression of fibrotic markers	-	98
Rh4	Heart	Ang II-induced myocardial remodeling in mice	Ang II-induced NRCMs	Inhibited myocardial hypertrophy, inflammatory and oxidative stress	The activation of NFIL3 as a downstream regulator of Rh4	92
Total ginsenosides	Lung	bleomycin-induced pulmonary fibrosis in rat	-	Enhanced the histological and morphometric image of the lung.	The inhibition of NF-κB immunoexpression	113

way [114]. AD-2 inhibits inflammatory response and HSC activation by regulating the Raf-MEK signaling pathway and VD/VDR axis, thereby improving hepatic fibrosis [52-54].

3.2. Clinical basis of ginseng therapy on fibrotic diseases and the need for more clinical studies

Tissue fibrosis is a chronic and complex disease with diverse triggers. The development of anti-fibrotic drugs presents significant challenges, and numerous clinical trials have been unsuccessful. Currently, approved drugs only decelerate fibrosis progression rather than provide a cure. In recent years, the U.S. Food and Drug Administration (FDA) has approved several medications for treating fibrosis, including nintedanib and pirfenidone for idiopathic pulmonary fibrosis, resmetirom for NASH-related liver fibrosis, and orkambi for cystic fibrosis. These medications demonstrate varying degrees of efficacy in alleviating patients' fibrotic symptoms in clinical applications. However, nintedanib, an approved drug for treating idiopathic pulmonary fibrosis, is associated with common side effects such as diarrhea, nausea, vomiting, and abnormal liver function and may also cause embryo-fetal toxicity. Pirfenidone, widely used to mitigate symptoms in idiopathic pulmonary fibrosis, commonly causes mild to moderate gastrointestinal reactions, rash, and alterations in liver function indicators. Resmetirom, the first FDA-approved drug for the treatment of NASH and related liver fibrosis, occasionally causes diarrhea and nausea during treatment. Orkambi, a clinically approved treatment for cystic fibrosis, has demonstrated efficacy in managing the disease; however, it is associated with adverse effects such as respiratory issues, gastrointestinal disturbances, and skin rashes. These side effects underscore the urgent need for the development of safer and more effective therapeutic options for fibrotic diseases. In contrast to Western medicine, TCM provides a unique and holistic approach to treating complex and chronic conditions, utilizing multi-target strategies that have shown significant advantages in addressing such diseases. Notably, total ginsenoside has exhibited superior safety and therapeutic profiles compared to pirfenidone in preclinical studies [124]. Clinical trials have demonstrated that both ginseng and patent medicine with ginseng as the principal ingredient have shown

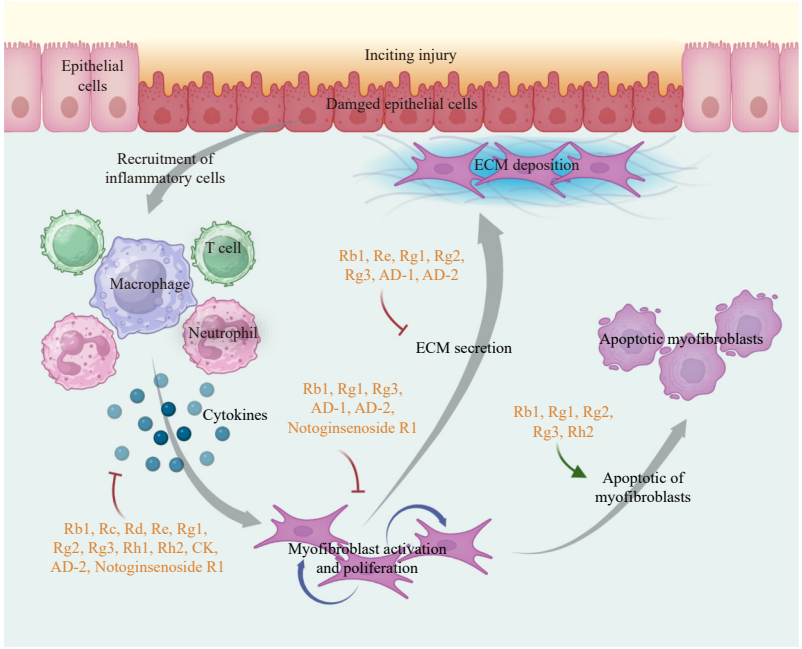

Fig. 2 Cellular injury, fibrogenesis, and the anti-fibrotic properties of ginsenosides. Following extracellular injury, endothelial damage triggers an inflammatory response that initiates a complex cascade of cellular and molecular events. Central to this process is the recruitment of circulating inflammatory cells, particularly macrophages and neutrophils. These cells secrete a variety of cytokines and chemokines, which amplify the wound-healing response and stimulate the activation and recruitment of fibroblasts and myofibroblasts. These cells proliferate rapidly in response to cytokine signaling and contribute to the production of extracellular matrix (ECM) proteins. In the case of chronic injury, myofibroblasts persist at the injury site, leading to excessive ECM accumulation and the eventual formation of fibrosis. Ginsenosides modulate this fibrotic process by negatively regulating key stages, as indicated by the dashed lines in the diagram. Abbreviations: ECM: extracellular matrix. The figure is created using BioRender.com.

promising effects in improving tissue fibrosis. A randomized controlled trial performed by Choi et al. suggests the potential of Korean Red Ginseng as a complementary therapy for chronic hepatitis B, indicated by the decreased level of non-invasive fibrosis serologic markers. including hyaluronic acid and TGF-β [125]. Yang conducted a clinical trial investigating the liver fibrosis-improving effect of Ginseng and Turtle Shell Decoction Pill on patients with chronic hepatitis B. The results revealed that treatment with Ginseng and Turtle Shell Decoction Pill significantly downregulated the serum levels of fibrotic indicators--hyaluronic acid and laminin [126].

While numerous studies have confirmed the anti-fibrotic effects of ginsenosides, current research on ginsenosides and fibrosis faces several limitations. Preclinical studies typically employ a single animal model, which can only represent fibrosis induced by specific etiologies. This approach limits the comprehensive evaluation of ginsenosides' efficacy against fibrosis diseases caused by various factors, thereby constraining the ability to predict their potential clinical applications fully. In current studies, the dosage of ginsenosides in animal models generally ranges from 10 to 20 mg·kg^{-1} which translates to a human equivalent dose of approximately 66 to 132 mg daily. Using ginsenoside Rb1 as an example, the Chinese Pharmacopoeia stipulates that the content of ginsenoside Rb1 in *Panax ginseng* should not be less than 0.18%. Consequently, this corresponds to a daily intake of 36.6 to 73.2 g of ginseng. However, the Chinese Pharmacopoeia recommends a daily intake limit for ginseng of 3 to 9 g, indicating that the dosage of ginsenosides in current research significantly exceeds the standard for human consumption.

Clinical applications of ginsenosides for attenuating fibrotic diseases have not yet been reported. The transition from preclinical to clinical studies faces challenges related to bioavailability, including limited membrane permeability, instability in the gastrointestinal tract, and hepatic first-pass effect. The low bioavailability of ginsenosides also presents significant obstacles to pharmacological studies. Firstly, the beneficial effects observed with some ginsenosides may be attributed to their metabolites produced by gut microbiota rather than the parent compounds themselves. Secondly, as compounds with low bioavailability, their distribution within the body must be considered, as they may not achieve sufficient concentrations in target organs. To overcome these issues, strategies involving modified dosage forms need to be introduced. When administered as liposomes, ginsenosides demonstrated a prolonged duration of action and slower metabolic rates [127]. Solid dispersions or inclusion complexes increased drug dissolution rates [128,129]. Microemulsions enhanced targeting capacity and reduced first-pass effects [130]. Microspheres facilitated targeted delivery and maintained stable ginsenoside concentrations through sustained release [131]. Based on current studies, liposomes show promising potential for developing new ginsenoside formulations. Although no ginsenoside liposomes have entered clinical research, liposomal formulations of other drugs have the highest number of clinical trials among new dosage forms, indicating significant potential. A review summarized research on ginsenoside delivery systems, with liposomes most frequently reported to have improved properties[132]. Liposomes offer various advantages in ginsenoside delivery, including improved solubility, increased free concentration in the vascular system, prolonged circulation time, and targeted delivery [132,133]. While these new formulations effectively improve ginsenoside bioavailability, poor stability and storage difficulties still limit their application. Further optimization and development of these dosage forms are necessary to enable widespread clinical use of ginsenosides for various diseases, thereby maximizing therapeutic effects. It is important to note that safety issues of finished dosage forms must be addressed concurrently.

Hemolysis is a characteristic of certain ginsenosides, presenting a significant challenge to their use as injectable medications. While total ginsenosides do not exhibit hemolytic effects, purified ginsenoside monomers demonstrate contrasting hemolytic and anti-hemolytic properties. Research indicates that PPT and its associated monomer ginsenosides display similar anti-hemolytic effects. Conversely, PPD promotes hemolysis, with its monomer ginsenosides showing considerable variation in hemolytic properties. Specifically, Rh2 and Rg3 initiate hemolysis, while other PPD-type ginsenosides offer varying degrees of protection against hemolysis in human erythrocytes [134]. To mitigate the hemolytic properties of ginsenosides, two approaches can be considered. Firstly, drug delivery systems such as nanoparticles, liposomes, or other micro/nanocarriers can encapsulate ginsenosides, reducing their direct interaction with red blood cell membranes and thereby inhibiting hemolysis [135]. Secondly, studies have demonstrated that oral administration of Rh2 in animal models can elicit pharmacological effects. Therefore, altering the administration method to oral intake represents a viable strategy to prevent direct entry into the bloodstream.

3.3. Discovery of new anti-fibrotic agents and target identification

Notably, ginsenoside shares a steroid structure with cholesterol [136], both possessing a basic core of cyclopentane polyhydroxy phenanthrene. Consequently, like cholesterol, ginsenosides demonstrate significant agglutin ability towards phospholipid vesicles, a crucial step in membrane fusion, adhesion, and cellular communication [137]. This characteristic may explain the facile absorption and subsequent potent effects of ginsenosides in various diseases. Ginsenosides, primarily dammarane-type sapogenins, are classified into PPD and PPT types based on structural features [138]. Currently, research on the structure-activity relationship of ginsenosides is predominantly focused on anti-tumor applications [139], possibly due to the field's prominence in drug development and the relative simplicity of cell models and detection indicators. Analysis of the structure-activity relationship in anti-tumor effects reveals that ginsenoside activity tends to increase as the number of sugar moieties linked to aglycone skeletons decreases. For ginsenosides with equal sugar moieties, those with sugar linkage at C-20 exhibit stronger anti-tumor activity [139]. Indeed, ginsenoside Rg3, containing only two glucose moieties, may owe its broad and potent anti-fibrosis effect to this characteristic. Similarly, ginsenoside Rg1, with a single glucose moiety at both C-6 and C-20, has become a prominent compound among PPT-ginsenosides. Research on the structure-activity relationship of ginsenosides in their anti-fibrotic effects is currently limited. Studies indicate that the anti-fibrotic effects of ginsenosides are primarily influenced by the number of hydroxyl moieties, the orientation of the hydroxyl group at C-20, and the number of sugar residues at C-3 [140,141]. In terms of anti-fibrotic properties, it has been observed that the PPD type, the S -configuration of the hydroxyl moiety at C-20, and the presence of only a glucose residue at C-3 are significant inhibitory elements on HSC-T6 cell proliferation [141]. To date, over 150 ginsenosides have been identified from ginseng, necessitating further studies to verify the pharmacological roles of more ginsenosides, particularly rare ones, in fibrotic diseases [26]. Future research should focus on elucidating the structure-activity relationship of ginsenosides in anti-fibrotic effects. Such studies can aid in predicting the activity of newly discovered ginsenosides to identify potential anti-fibrotic agents. Additionally, the structure of candidate ginsenosides can be modified based on these relationships to optimize their efficacy.

Based on our summary, the phenotypes observed in anti-fibrosis studies of ginsenosides are relatively consistent, with a common set of fibrosis indicators shared across various organs. These indicators typically include the expression of proteins related to collagen synthesis and the activation of the TGF-β1 pathway. In recent years, there has been an increasing application of chemically synthesized probes for non-invasive disease detection.

For fibrotic diseases, several studies have developed probes targeting Col I and other markers, demonstrating promising detection results in both clinical studies and preclinical models [142, 143]. Consequently, future research on the anti-fibrotic effects of ginsenosides could benefit from incorporating these probes as novel indicators. Furthermore, these probes may be utilized in structure-activity relationship studies, complementing traditional indicators to enhance our understanding of ginsenoside efficacy.

While numerous studies have explored the anti-fibrotic effects of various ginsenosides, the majority focus primarily on determining their impact on fibrotic markers and downstream classic pathways. There is a notable scarcity of research identifying the specific molecular targets of ginsenosides. The target fishing strategy, widely employed to identify downstream molecular targets of pharmacologically effective chemical compounds, offers a promising approach. This method involves creating probes from compounds and subsequently identifying bound proteins through chemical proteomics [144]. Five distinct probe types with diverse molecular structures have been developed, each with its own target fishing method for screening small molecule targets. These categories include immobilized, activity-based, click chemistry, photoaffinity, and non-labeling probes. Quantitative proteomics approaches primarily encompass stable isotope labeling by amino acids in cell culture, chemical labeling approaches, and label-free approaches [145]. The application of such strategies in future research holds significant potential for identifying the direct targets of ginsenosides.

Ginsenosides demonstrate significant effects on various diseases through the action of gut microbiota [146-148]. The gut microbiota can become dysregulated under the influence of diverse external stimuli, resulting in an increase of harmful gut microbiota metabolites. These metabolites may reach tissues *via* the bloodstream, potentially inducing fibrogenesis. Notably, the gut microbiota can metabolize ginsenosides. Certain gut bacteria contain glycosidases capable of hydrolyzing the sugar chains of ginsenosides, forming ginsenosides with reduced sugar moieties or deglycosylated ginsenosides, which may influence their anti-fibrotic effects. Consequently, the gut microbiota presents a potential target for enhancing the therapeutic effects of ginsenosides. For instance, Rk3 supplementation has been shown to modulate the composition of the intestinal microbiota, reducing the abundance of deleterious bacteria, such as *Firmicutes*, while increasing the richness of beneficial bacteria. Rk3 treatment also significantly mitigated the elevation of acetic acid, propionic acid, and isobutyric acid produced by *Firmicutes*, thereby alleviating liver inflammation, lipid deposition, and fibrosis in NASH [148]. Furthermore, gut microbiota and its metabolites have been identified as biomarkers of tissue fibrosis [149]. Given these findings, further research is warranted to explore whether other ginsenosides exert anti-fibrotic effects through regulation of the gut microbiota and its metabolites.

In conclusion, ginsenosides demonstrate significant therapeutic potential as natural compounds for the prevention and treatment of fibrotic diseases. Further research on ginsenosides is necessary to enhance anti-fibrosis strategies across various organs, potentially contributing to the improvement of organ function in affected patients.

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Declaration of competing interest

These authors have no conflict of interest to declare.

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