Short Review

Ginsenosides: potential therapeutic source for fibrosis-associated human diseases

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A B S T R A C T
Tissue fibrosis is an eventual pathologic change of numerous chronic illnesses, which is characterized by resident fibroblasts differentiation into myofibroblasts during inflammation, coupled with excessive extracellular matrix deposition in tissues, ultimately leading to failure of normal organ function. Now, there are many mechanistic insights into the pathogenesis of tissue fibrosis, which facilitate the discovery of effective antifibrotic drugs. Moreover, many chronic diseases remain a significant clinical unmet need. For the past five years, many research works have undoubtedly addressed the functional dependency of ginsenosides in different types of fibrosis and the successful remission in various animal models treated with ginsenosides. Caveolin-1, interleukin, thrombospondin-1 (TSP-1), liver X receptors (LXRs), Nrf2, microRNA-27b, PPAR-STAT3, liver kinase B1 (LKB1)-AMPK, and TGF-β1/Smads are potential therapy targeting using ginsenosides. Ginsenosides can play a targeting role and suppress chronic inflammatory response, collagen deposition, and epithelial–mesenchymal transition (EMT), as well as myofibroblast activation to attenuate fibrosis. In this report, our aim was to focus on the therapeutic prospects of ginsenosides in fibrosis-related human diseases making use of results acquired from various animal models. These findings should provide important therapeutic clues and strategies for the exploration of new drugs for fibrosis treatment.

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1. Introduction

1.1. The mechanisms of fibrosis in tissues

Fibrosis is a familiar character of numerous organ-targeted diseases and is one of the main causes of mortality and morbidity in countless patients worldwide. It is considered that almost half of human mortality is associated with fibrosis-associated disorder [1]. Fibrosis is regarded as the abundant deposition of extracellular matrix (ECM) including collagen and fibronectin around injured tissue, which can cause distortion of tissue architecture, loss of organ function, and, finally, death, as seen in end-stage liver, kidney, lung, and heart diseases [2]. This pathology ordinarily begins as an abnormal wound repair process response to repeated or chronic tissue damage, regardless of the underlying pathogenesis, and can occur in virtually any solid organ or tissue [3].

In general, wound healing experiences three broad phases that are temporally overlapping but functionally distinct [4,5]. In a normal situation, following injury, hemostasis is achieved through the formation of a platelet plug and a provisional ECM, accompanied by the threshold of inflammation and recruitment of immune cells. This process initiates the first phase of healing, namely the inflammatory phase. There are much more neutrophils and macrophages infiltration in tissues, which combat possible infections and remove tissue and cell debris. In the inflammatory phase, impaired endothelial cells, epithelial cells, and myofibroblasts produce aberrant matrix metalloproteinases (MMPs) to disrupt basement membrane in local tissues and discharge various cytokines and chemokines, which recruit and activate more different immune cells, including neutrophils, macrophages, T lymphocyte cells, and B lymphocyte cells. These activated leukocytes release proinflammatory, vasoactive, and profibrotic effectors, including transforming growth factor (TGF)-β1, tumor necrosis factor (TNF)-α, and platelet-derived growth factor (PDGF), as well as interleukin (IL)-6 and IL-13, to prompt the proliferative phase of healing [6–9]. It is generally accepted that TGF-β1 has a particularly conspicuous
role in inducing the differentiation of precursor cells into myofibroblasts, which rapidly generate a tremendous amount of ECM to maintain the integration of the injured tissue during repair and to improve cell proliferation for the formation of granulation tissues [10]. In the final tissue remodeling and cell maturation phase, activated myofibroblasts provoke the wound contraction; the provisional ECM is degraded and remodeled to rebuild the parenchymal tissue architecture. However, life is not always what we want it to be. An abnormal tissue reconstruction process is more common and can be featured by persistent inflammatory response, necrocytosis, sustained myofibroblasts activation, excessive ECM deposition, and finally a perpetual fibrotic lesion formation (Fig. 1). In most of the cases, chronic inflammation always can lead to tissue fibrosis, which initiates the generation of profibrotic growth factors [5]. In addition to this, aging also is recognized to result in fibrosis in diverse organs [11]. Interestingly, genetic factors are found to cause cystic fibrosis [12] and idiopathic pulmonary fibrosis [13].

1.2. Ginseng and ginsenosides

The term “Ginseng” is interpreted from the Chinese “人参” and is extensively used as a restorative drug and generally means Asian ginseng. It has been highly acclaimed in China for more than two thousand years. The Panax family consists of at least nine kinds of ginseng, such as Panax quinquefolius, Panax notoginseng, Panax japonicus, Panax vietnamensis, and Panax trifolius [14].

There are three vital ingredients in ginseng: polysaccharides, saponins, and phenolic compounds [15]. It has been reported that a four year-old Korean ginseng contains ~5% polysaccharides, ~3% saponins, and ~0.4% phenolic compounds [16]. Among these elements, saponins have been comprehensively explored and confirmed to trigger various biological effects. Ginsenosides, conventionally identified as saponins, are regarded as the primary bioactive constituents of ginseng [17]. Saponin is a kind of triterpenoidal dammarane glycosides, called ginsenosides Rx in line with their ability to move on TLC plates, with a decline of polarity from “a” to “h” [18]. Based on the location of sugar moieties, ginsenosides can be distinguished into protopanaxadiol type (I-1 type) and protopanaxatriol type (I-2 type). Until now, researchers have identified more than 80 ginsenosides [18]. Among them, ginsenosides Rb1, Rb2, Rg1, Rg2, Rc, Rd, and Re are major ingredients of white and red ginsengs, whereas ginsenosides Rg3, Rg5, and Rg6 are well known to be uniqueness of Korean Red Ginseng (KRG). Table 1 overviews the anti-fibrosis performances of canonical ginsenosides. These contents will be investigated in detail in the latter sections.

1.3. Ginsenosides and their therapeutic potential

Many phytochemicals are noted to be anti-cancer candidates in accordance with their low toxicities and their inhibitory effects on inflammation [19]. Previous research works have revealed that consumption of ginseng is closely associated with reduced risk of cancer and good cancer therapeutic effect. The data from case-control studies have indicated that periodical consumption of ginseng could effectively inhibit the development of oral squamous cell cancer, gastric cancer, liver cancer, lung cancer, ovarian cancer, pancreatic cancer, and colorectal cancer [20,21]. A retrospective cohort study including about 4600 healthy individuals found that using ginseng regularly obviously decreased the occurrence of tumor [22]. Results from an epidemiological research of breast cancer showed that periodical usage of ginseng before and after cancer diagnosis could remarkably decrease the risk of tumor recurrence and death from cancer [23]. Likewise, a recent preliminary work demonstrated that taking 800 mg of Panax ginseng each day could effectively improve fatigue caused by cancer [24].

Fig. 1. The cellular and molecular mechanisms of fibrosis and anti-fibrotic property of ginsenosides. Once an injury occurs in an organ, impaired epithelial and/or endothelial cells secrete chemokines and growth factors. Macrophages and monocytes are recruited and activated, which further result in the release of cytokines and chemokines, and finally induce fibroblast activation. Activated fibroblasts transform into myofibroblasts and actively synthesize ECM. Once chronic injury, inflammation, and necrosis occur, myofibroblasts are persistently activated and excessive ECM is deposited, finally leading to fibrosis formation. Ginsenosides negatively regulate fibrosis. Red blunted line: an inhibitory effect of ginsenosides on secretion of proinflammatory cytokines from immune cells or injured tissue; blue blunted line: an inhibitory effect of ginsenosides on myofibroblast differentiation, proliferation, and activation; green blunted line: an inhibitory effect of ginsenosides on excessive ECM accumulation and fibrosis formation. Abbreviation: EMT, epithelial–mesenchymal transition; ECM, extracellular matrix.
| Ginsenosides | Model | Animal/cell type | Therapeutic target | Output (except fibrosis) | Refs |
|-------------|-------|-----------------|-------------------|---------------------------|------|
| Liver fibrosis | Rb1 | CCl4 | Sprague–Dawley rats | The inhibition of hepatic prostaglandin E2 and TIMP-1 | Decreased plasma and hepatic triglyceride, hepatic cholesterol; inhibited IL-1β concentrations and abnormal lipid metabolism; alleviated HFD-induced insulin resistance | [40] |
| | Compound K and/or Rh1 | Non-alcoholic fatty liver | Sprague–Dawley rats | The inhibition of HSCs proliferation and activation; the induction of HSCs apoptosis | Improved hepatic function and abnormal lipid metabolism; alleviated HFD-induced insulin resistance | [50] |
| | Rg1 | Thioacetamide | Sprague–Dawley rats | The inhibition of PDGF-induced proliferation, activation of HSCs, and ROS formation, and NF-κB binding activity | Decreased hepatic hydroxyproline content and lipid peroxidation | [46] |
| | 25-OCH₃-PPD | Thioacetamide | C57BL/6 mice; rats HSC-T6 cells | The inhibition of LXRs-P2X7R-mediated NLPR3 inflammasome | Improved hepatic function, inhibited HSCs activation and hepatocyte apoptosis, and proinflammatory cytokines | [43] |
| | Rg1 | Alcohol- and CCl4 | Wistar rats; Primary HSCs of rats | The activation of Nrf2 pathway | Improved liver function; inhibited liver inflammation and HSCs activation; decreased lipid peroxidation and modified antioxidant enzyme activity | [47] |
| | Rb1 | H₂O₂ | Rats HSC-T6 cells | The inhibition of collagen, TGF-β1, MMP-2, and TIMP-1 | Decreased HSCs proliferation and activation | [48] |
| | 25-OCH₃-PPD | 10% FBS (primary HSCs) | Human LX-2 cells | Human LX-2 cells | The activation of LKB1-AMPK pathway Induced HSCs apoptosis and promoted oxidative stress | [52] |
| | 25-OCH₃-PPD | Thioacetamide | Primary HSCs of mice; Kunming mice | The inhibition of JNK and p38-ERK pathway | Decreased the release of inflammatory cytokines | [44] |
| | Rg1 | CCl4 | Kunming mice; rats HSC-T6 cells | The inhibition of the TGF-β1/Smad pathway and the activation of Nrf2 | Induced HSCs apoptosis and inhibited intracellular ROS level | [51] |
| Cardiac fibrosis | Rg1 | TAC | Sprague-Dawley rats | The inhibition of p38 MAPK and the activation of phospho-Akt pathway | Decreased left ventricular hypertrophy; enhanced myocardial angiogenesis [58] |
|-----------------|-----|-----|---------------------|------------------------------------------------------------------|--------------------------------------------------------------------------|
| Rb1             | Abdominal aortic coarctation | Sprague-Dawley rats | The inhibition of TGF-β1/Smad and ERK signaling pathway and the activation of Akt pathway | Improved cardiac function; decreased cardiac hypertrophy; decreased mitochondrial membrane potential; enhanced the translocation of GLUT4 [63] |
| Rg1             | CTEPH | Sprague-Dawley rats | The regulation of MMP-2 and -9 | Decreased right ventricular hypertrophy and immune cell infiltration [59] |
| Rh2             | STZ | Sprague-Dawley rats; rat H9C2 cells | The regulation of PPAR-δ-STAT3 pathway | Improved cardiac function; decreased superoxide ions produced by high glucose [65] |
| Rb1             | STZ | Wistar rats; rats primary fibroblast | The inhibition of TGF-β1/Smad pathway and the promotion of Smad7 | Improved cardiac function; inhibited cardiac fibroblast to myofibroblast differentiation [70] |
| Re              | Isoproterenol | Wistar rats | The inhibition of TGF-β1/Smad3 pathway | Decreased heart failure; improved cardiac function [66] |
| Rg1             | Doxorubicin | C57BL/6J mice | The inhibition of ER stress and autophagy | Improved cardiac function; inhibited cardiac autophagy [60] |
| Rb3             | CVB3 | Primary CMVECs of rats | The regulation of Pyk2-PI3K-Akt pathway | Attenuated oxidative stress and preserved endothelial function [68] |
| Rd              | Pressure overload | C57BL/6 mice; primary cardiac myocytes of rats | The inhibition of ERK and TGF-β1 pathways and the activation of Akt pathway | Improved cardiac function; decreased cardiac hypertrophy; decreased inflammation and oxidative stress [67] |
| Renal fibrosis  | Rg1 | UUO | Sprague-Dawley rats | The regulation of the Klotho/TGF-β1/Smad pathway | Improved kidney function; prevented EMT [76] |
| Rb1 and Rc      | Cyclosporine A | C57BL/6J mice; human HK-2 cell line | The regulation of oxidative stress pathway | Improved kidney function; inhibited inflammation and the production of proinflammatory cytokines; prevented tubular epithelial cell apoptosis [81] |
| Rg1             | DN | Wistar rats | The inhibition of TGF-β1/Smads pathway and oxidative stress | Decreased BUN and Scr; increased anti-oxidative capacity [78] |
| Rg1             | UUO | Sprague-Dawley rats | The inhibition of ER stress and unfolded protein response-related apoptotic pathway | Improved renal function; activated ER stress response [75] |
| Rg1             | Cyclosporine A | Sprague-Dawley rats | The inhibition of ER stress-triggered tubular cell apoptosis | Decreased tubular epithelial cell apoptosis [79] |
| Rg1             | UUO | Sprague-Dawley rats | The regulation of thrombospondin-1 and VEGF expression | Decreased microvessel density; improved tubular atrophy [74] |
| Rb1             | UUO | Sprague-Dawley rats | The regulation of oxidative damage and TGF-β1 expression | Increased urinary heme oxygenase-1 level; decreased p47phox expression [73] |
| Rg1             | TGF-β1 | Rats NRK-52E cells | The inhibition of ERK pathway | Inhibited the process of EMT [82] |
| Rg1             | UUO | Sprague-Dawley rats | The inhibition of TGF-β1/Smads pathway and thrombospondin-1 expression | Inhibited tubular EMT [72] |

(continued on next page)
| Ginsenosides | Model | Animal/cell type | Therapeutic target | Output (except fibrosis) | Refs |
|-------------|-------|-----------------|--------------------|-------------------------|------|
| Lung fibrosis | Rg1 | Bleomycin | Sprague-Dawley rats | The regulation of TGF-β1 and Caveolin-1 | Decreased lung injury, inflammatory cell infiltration [87] |
| | Rg1 | COPD | Sprague-Dawley rats; human MRC5 fibroblasts | The inhibition of TGF-β1/Smads pathway | Decreased emphysema; inhibited immune cell infiltration; prevented lung fibroblast transdifferentiation [88] |
| Total ginsenoside | Bleomycin | BALB/c mice | The inhibition of TGF-β1/Smad pathway and the promotion of Smad7 | Reduced the pulmonary coefficient; regulated the MMPs system [89] |
| Other fibrotic diseases | Rg3 | Rabbit-ear HS | Primary human HSFs; rabbits | The regulation of collagen fibers accumulation and VEGF expression | Inhibited HS fibroblasts proliferation and induced apoptosis; limited inflammation [90-93] |
| | Rg3 | Keloid scar | Primary human keloid fibroblasts | The inhibition of TGF-β1/Smads and ERK pathway | Inhibited the proliferation, migration, invasion and angiogenesis of keloid fibroblasts [94] |
| | Rb1 | Rabbit-ear HS | Rabbits | The inhibition of profibrotic proteins and growth factors | Inhibited cell proliferation, invasion; regulated MMPs expression [95] |
| | Rg3 | Endometriosis | C57BL/6 mice; Primary human HESCs and Ishikawa Cells | The modulation of miR-27b-3p expression | Inhibited cell proliferation and invasion; regulated MMPs expression [97] |

Abbreviations: CCl4, carbon tetrachloride; TIMP-1, tissue inhibitor of metalloproteinase-1; IL-1β, interleukin-1β; HSCs, hepatic stellate cells; HFD, high fat diet; PDGF, platelet-derived growth factor; ROS, reactive oxygen species; NF-κB, nuclear factor-κB; LXR, liver X receptor; P2X7R, P2X7 receptor; TGF-β1, transforming growth factor-β1; MMP-2, matrix metalloproteinase; FBS, fetal bovine serum; LKB1, liver kinase B1; AMPK, AMP-activated protein kinase; JNK, c-Jun N-terminal kinase; TAC, transverse aortic constriction; MAPK, mitogen-activated protein kinase; GLUT4, glucose transporter type 4; CTEPH, chronic thromboembolic pulmonary hypertension; STZ, streptozotocin; PPARα, peroxisome proliferator-activated receptor α; STAT3, signal transducer and activator of transcription 3; ER, endoplasmic reticulum; CVB3, coxsackievirus B3; UUO, unilateral ureter obstruction; EMT, epithelial–mesenchymal transition; DN, diabetic nephropathy; BUN, blood urea nitrogen; Scr, serum creatinine; VEGF, vascular endothelial growth factor; COPD, chronic obstructive pulmonary disease; MMPs, matrix metalloproteinase; HS, hypertrophic scarring; HSC: hepatic stellate cell line; LX-2: human hepatic stellate cell line; H9C2: embryonic cardiomyocytes cell line; CMVECs: cardiac microvascular endothelial cells; HK-2: human renal proximal tubular cells; NRK-52E: rat renal tubular epithelial cells; MRC5: human embryonic lung fibroblasts; HSFs: hypertrophic scar fibroblasts; HESCs: human endometrial stromal cells.
years, most of the effective anti-tumor constituents in the ginseng have been identified, like ginsenosides Rg3 and Rh2 [25,26]. Ginsenosides have been accepted and emphasized as a potential choice for anticancer treatment. In China, even worldwide, some of them are easy to buy as nonprescription drugs at the pharmacy. In addition, ginseng has been generally considered as safe and is extensively used in the United States and Europe. Apart from showing anticancer attributes, ginsenosides successfully alleviate the progression of atherosclerosis [27], myocardial ischemia/reperfusion injury [28], inflammation [29], and Alzheimer’s [30], Parkinson’s [31], and fibrosis-related diseases.

Fibrosis represents a normal physiological response following injury, but uncontrollable production and accumulation of fibrous ingredients destroys the normal tissue structure and organ function [32]. Thus, it is important to sustain organ physiological function through fibrosis control appropriately. Until now, a few commercial agents have been observed to exert inhibitory effects on fibrosis, such as angiotensin II type 1 receptor blockers (ARB), angiotensin converting enzyme inhibitors (ACEI), metformin, and MMP inhibitors [33–35]. Despite these drugs exhibit certain efficacy against fibrosis, progressive organ dysfunction still occurs in most patients. It is imperative to develop new alternative therapeutics and strategies to relieve fibrosis for clinicians. This review describes recent experimental results of ginsenosides that specially target inflammatory mediators or fibrosis-related signaling pathways and summarizes the possible benefits of ginsenosides as novel regulators of tissue fibrosis.

2. Experimental outcomes of ginsenosides in fibrotic diseases

2.1. Liver fibrosis

Progressive liver fibrosis is one of the hallmark traits of liver impairment, which is a primary reason of mortality in patients with different chronic liver diseases [36]. Liver fibrosis will evolve into liver cirrhosis along with the condition progress, and ultimately patients receive organ transplantation [37]. Chronic hepatic inflammation from chronic hepatitis virus infections, abnormal lipid metabolism, and alcohol abuse contributes to aberrant accumulation of collagen and ECM proteins, finally rising up to severe fibrosis and progression to cirrhosis. In 2009, Peng et al found that the degree of liver fibrosis and collagen deposition area in tissue were strikingly attenuated after Panax notoginseng saponins (PNS) treatment. PNS treatment significantly reduced the generation of growth factors and pro-inflammatory cytokines, whereas elevated the production of anti-inflammatory cytokines [38]. Among more than 30 ginsenosides, ginsenoside Rb1 (C_{45}H_{92}O_{23}) is regarded as the richest ginsenoside in Panax ginseng [39]. A study from Hou et al showed that ginsenoside Rb1 attenuated liver fibrosis by preventing fat deposition, secretion of pro-inflammatory factors, whereas elevated the production of anti-inflammatory cytokines [38].
LXRs were reported to be able to promote the resolving of hepatic fibrosis and inflammation through targeting genes involved in cholesterol and lipid metabolism [42]. In addition, 25-OCH₃-PPD was found to inhibit the formation and activation of the NLRP3 inflammasome in liver fibrosis [43]. Notably, Su and co-workers supplemented another piece of data that supported the inhibitory effect of 25-OCH₃-PPD on inflammation and liver fibrosis [44]. Their findings in combination with previous observations further confirm an advantageous benefit of 25-OCH₃-PPD in liver fibrosis treatment.

It is generally known that hepatic stellate cells (HSCs) belong to primary effector cells of fibrosis located perisinusoidally around the space of Disse in liver injury. As one of the pro-fibrogenic cells, HSCs can be activated from quiescent cells to myofibroblast-like cells under inflammatory microenvironment. Activated HSCs further lead to the excessive accumulation of ECM [45]. Thus, how to control the proliferation and activation of HSCs is considered the vital issue for liver fibrosis treatment. Data from rats treated with TAA and cultured HSCs stimulated by PDGF-BB showed that ginsenoside Rg1 significantly prevented HSCs’ proliferation and activation, as well as oxidative stress response. Ginsenoside Rg1 reduced PDGF receptor-β expression via down-regulating the nuclear factor-kB activity [46]. Furthermore, in alcohol and CCl₄-induced rat liver fibrosis model, activated HSCs and liver inflammation were dramatically decreased in the Rg1-treatment group. The protective effect of Rg1 against fibrosis is related with the upregulation of nuclear translocation of Nrf2 and antioxidant enzymes (SOD, GSH-Px, and CAT) [47]. Moreover, ginsenoside Rb1 was also found to have a prominent inhibitory effect on HSCs by regulating the proliferation and activation, as well as collagen and TGF-β1 expression [48].

Fig. 3. Overall protection of ginsenosides against fibrosis in various organs and tissues. Collectively, ginsenosides exert comprehensive protective effects against fibrosis in various organs and tissues, including heart, liver, lung, kidney, etc. These findings demonstrate that ginsenosides may contribute to protection and recovery of multiple organs and tissues after injury. CCl₄, carbon tetrachloride; COPD: chronic obstructive pulmonary disease; TGF-β1: transforming growth factor beta 1.
Apoptosis of activated HSCs is thought to be the main molecular biological mechanism in the resolution of fibrosis [49]. Chen et al clearly demonstrated that treatment with ginsenoside R1 and Compound K either in combination or alone markedly alleviated the liver dysfunction and liver fibrosis caused by high fat diet, which were associated with decreased proliferation and activation of HSCs, and increased HSCs apoptosis [50]. Ginsenoside Rg1 was observed to significantly reduce HSCs proliferation, reverse epithelial–mesenchymal transition (EMT) induced by TGF-β1, and stimulate apoptosis in CCI4-induced liver fibrotic model. Mechanistically, ginsenoside Rg1 shows up a protective action on liver fibrosis via down-regulating the TGF-β1/Smad pathway and promoting Nrf2 nuclear translocation [51]. Park et al prepared LX-2 cell line and primary HSCs from patients with ginsenoside 20S-protopanaxadiol and observed the change of HSCs number. 20S-protopanaxadiol significantly induced more apoptosis of HSCs through activating LKB1 and the downstream AMPK pathway, indicating it could be a therapeutic candidate for liver fibrosis treatment [52]. Ding et al found that saponins of Panax japonicus distinctly ameliorate liver dysfunction and reduce collagen fibers formation and immune cell infiltration in the fatty liver fibrosis model through the inhibition of the endoplasmic reticulum stress (ERS) and the regulation of inflammation and apoptosis pathways [53].

2.2. Cardiac fibrosis

Cardiac fibrosis is featured by the excessive deposition of ECM-related proteins in the myocardium. It is an essential pathophysiological process existing in nearly all types of cardiac diseases [54]. Cardiac fibrosis damages myocardial structure, disturbs myocardial excitation–contraction coupling, disrupts diastolic and systolic blood pressure, ultimately resulting in the progress of cardiac diseases to heart failure [55,56]. It has been confirmed that the extent of cardiac fibrosis sustains a significant opposite interrelation with outcome, and until now, the only effective treatment for end-stage fibrotic disease is organ transplantation. Considering the limited usability of organ transplantation, the discovery of alternative pharmacologic strategies is still the first priority for researchers.

Ginsenosides have been found to play multiple pharmacological roles on the cardiovascular system [57]. Up to now, most of the previous researches have focused on ginsenoside Rg1. Zhang’s group revealed that Rg1 administration significantly decreased transverse aortic constriction (TAC)-induced myocardial fibrosis and left ventricular hypertrophy and maintained myocardial function and the relevant signaling pathways, including Akt and p38 MAPK pathway [58]. In addition, Rg1 also has the effect on the myocardial remodeling in chronic thromboembolic pulmonary hypertension model [59]. Furthermore, Xu et al found that Rg1 treatment could markedly inhibit the deterioration of myocardial function and myocardial fibrotic changes induced by Doxorubicin (DOX) [60]. Wei et al took advantage of polymeric carriers named gelatin microspheres to encapsulate Rg1 and crosslink with genipin, then injected into an infarcted myocardium rat model. Their results suggest that ginsenoside Rg1 as a stabilized angiogenic compound improves myocardial reperfusion and contributes to the maintenance of infarcted left ventricle function [61]. Recently, Li et al investigated the protective effect of Rg1 on myocardial remodeling in a subacute myocardial infarction mouse model, which is associated with down-regulation of α-SMA and MMP-9 [62].

Apart from Rg1, other ginsenosides (Rb1, Rh2, Re, and Rb3) have been described to have a protective action in cardiac function and remodeling. High dose of ginsenoside Rb1 plays an important role in cardiac remodeling via reducing the levels of cardiac fibrosis-related genes (including collagen I, angiotensin II, and periostin), restoring mitochondrial function, and elevating glucose uptake through augmenting GLUT4 translocation [63]. As we know, cardiovascular complications have become a major death reason in diabetic patients. Diabetic cardiomyopathy is primarily featured with cardiac fibrosis and consequent cardiac malfunction [64]. Lo et al [65] observed that increased heart weight/body weight ratio was decreased to a great degree by ginsenoside Rh2 in a streptozotocin (STZ)-stimulated type-1 diabetic rat’s model. However, the anti-fibrosis effects of Rh2 could be reversed by peroxisome proliferation-activated receptor δ (PPARδ) GSK660 administration, implicating that PPARδ signaling pathway may be involved in this process. In addition, GSK9206 or siRNA specific for PPARδ also was able to reverse Rh2-induced down-regulation of fibrosis-related signals, such as signal transducer and activator of transcription 3 (STAT3), fibronecrtin, and connective tissue growth factor (CCN2) in high glucose-cultured cardiomyocytes. Taking advantage of myocardial fibrosis animal models, Wang et al found that ginsenoside Re treatment could obviously decrease heart weight, myocardial fibrosis, and hydroxyproline content [66]. These effects might be associated with downregulation of TGF-β1 and Smad3 in cardiac tissue. A recently published research study reported that Rd remarkably prevented cardiac hypertrophy and fibrosis by pressure overload, fibrotic changes, and inflammation [67]. However, unlike the action mechanism of Rg1 [58], Rd improved cardiac remodeling and dysfunction primarily through regulating expression of p-Akt, p-ERK1/2, calcineurin A, and TGF-β1 [67]. Another interesting finding in the study from Yang et al [68] suggests that ginsenoside Rb3 can inhibit cardiac microvascular endothelial–mesenchymal transition following coxsackievirus B3 infection through regulation of the Pyk2/P3K/Akt pathway.

It is a common phenomenon for drug combinations in the practice of traditional Chinese medicine. “Fu fang” tonics composed by different herbs are often prescribed. This practice is similar to the drug cocktail strategy widely used in Western medicines. Shen et al [69] found that Shen Song Yang Xin Capsule (SSYX) inhibited diabetic myocardial fibrosis through preventing the TGF-β1/Smad3 pathway. Rb1 has been identified as the major ingredient of SSYX. Zhang et al [70] showed that Sheng Mai Yin (SMY) can reduce the risk of Adrionycin-induced myocardial fibrosis through down-regulation of inflammatory cytokines and MMPs. Rg1 has been recognized to be the major components of SMY. YiQiFuMai Powder Injection, redeveloped based on SMY, was found to alleviate coronary artery ligation -heart failure through ameliorating cardiac function, collagen deposition, and fibrosis via inhibition of MAPK signaling pathways. The major compounds in YiQiFuMai are ginsenosides and lignans. Broadly speaking, we found that ginsenosides are capable of regulating the development of cardiac fibrosis.

2.3. Renal fibrosis

Chronic kidney disease (CKD) influences billions of population globally and has high mortality. CKD can develop into end-stage kidney disease (ESKD), which is fatal without renal replacement therapy [71]. Kidney fibrosis is defined by aberrant production and accumulation of fibrous ingredients produced by renal fibroblasts. Kidney fibrosis frequently occurs after unilateral ureteral obstruction (UUO) [72–76], diabetic nephropathy [77,78] and cyclosporine A treatment [79–81]. Ginsenosides have shown to exert a renoprotective effect. Xie et al [72] found that ginsenoside Rg1 treatment obviously restrained interstitial fibrosis induced by UUO including tubular injury and collagen accumulation. Intriguingly, Rg1 significantly reduced α-SMA expression and simultaneously improved E-cadherin expression in the obstructed kidney and TGF-β1 induced rat tubular cells (NRK-52E), suggesting that the
underlying mechanism of anti-fibrosis might be partly associated with the reversal of tubular EMT [72,82]. Further study from the same UUO model demonstrated that Rg1 also could control renal microvascular integrity to prominently increase peritubular capillary densities through decreasing thrombospondin-1 (TSP-1) expression and increasing vascular endothelial growth factor (VEGF) expression [74]. Additionally, Li et al discovered more possible mechanism of Rg1 in the UUO model. They observed that Rg1 could prevent the renal fibrotic process partly by inhibition of ERS and unfolded protein response (UPR)-associated apoptotic pathway in UUO kidney [75]. Besides this, their results showed that Rg1 could reverse EMT and UUO-induced renal interstitial fibrosis through targeting the Klotho/TGF-β1/Smad pathway in UUO kidney [76]. In addition, our recent new evidence shows that Rg5 could prevent renal tubular cells autophagy by modulating the key proteins in the AMPK-dependent mTOR pathway, as well as the ERK and p38 MAPK pathway in vivo and in vitro (unpublished data).

Cyclosporine A (CsA), as a common clinical immunosuppressive agent, has been widely used for suppressing the rejection response after organ transplantation. Numerous experimental studies have shown that prolonged usage of CsA induces serious side effects, including progressive renal interstitial fibrosis, renal cell apoptosis, imunod cell infiltration, and hyalinosis of the arteriolar walls [83]. Doh's group [81] found that Korean Red Ginseng extract treatment could effectively inhibit deterioration of renal function, typical pathologic lesions, and apoptotic cell death through alleviating oxidative stress in a CsA nephropathy model and cell culture model in vitro. The major ingredients of KRC were ginsenoside Rb1 (8.27%) and Rc (3.90%). Following Doh's research, Lim et al further proposed that KRG extract exhibited an inhibitory effect on CsA-induced autophagosome formation and autophagic aggregates, which might be concerned with the activation of the Akt/mTOR pathway [80]. Moreover, ginsenoside Rg1 also clearly manifests the evident anti-apoptosis effect in a chronic CsA nephropathy rat model [79]. The protective actions of ginsenosides on diabetic nephropathy have been observed by several studies. Du et al [77] suggested that PNS administration could protect against kidney injury induced by diabetes possibly through enhancing SIRT1 and suppressing inflammation, as well as activating antioxidant motions. One study even found that ginsenoside Rg1 combination with Astragaloside IV was more effective on inhibiting oxidative stress response and down-regulating the activation of the TGF-β1/Smads signaling cascade in diabetic nephropathy rats [78]. Summarizing the results of the above stated, ginsenosides were suggested as an important option during the treatment of renal fibrosis.

2.4. Pulmonary fibrosis

Pulmonary fibrosis often leads to a chronic irreversible decline in pulmonary function. The leading reasons of pulmonary fibrosis include cigarette smoking, air pollution, and viral infection. Hitherto, no effective treatment has been identified that can restrict the development of pulmonary fibrosis [84]. A few studies have shown the therapeutic potential of ginsenosides in pulmonary fibrosis. Zhang and co-workers identified that PNS treatment apparently ameliorated the cardiopulmonary injury and reduced inflammatory response via regulating the NF-κB signaling pathway [85], which remains consistent with the finding from Tsai et al [86]. Zhan et al [87] showed clearly a remarkable effect of ginsenoside Rg1 on a bleomycin-induced pulmonary fibrosis animal model. Rg1 was found to decrease α-SMA and down-regulate TGF-β1, as well as up-regulate Caveolin-1. Guan et al [88] also confirmed an inhibitory effect of Rg1 in cigarette smoking-induced air fibrosis. Rg1 was found to restrain fibrosis progression through inhibiting the TGF-β1/Smad pathway in in vitro pulmonary fibroblasts and in vivo chronic obstructive pulmonary disease (COPD) rats. Likewise, total ginsenoside exhibits the protective effect on pulmonary fibrosis by bleomycin through interference of the TGF-β1/Smad signaling cascade and MMP system [89].

2.5. Miscellaneous diseases

Hypertrophic scars (HS), or keloids, are one of fibrosis-related disorders. It is hard to handle because surgical treatment or comparable interventions could generate tissue lesion aggravation. In spite of only a few studies mentioned, ginsenosides can be classified as potential therapeutic choices for HS or keloids. Cheng’s group confirmed that Rg3 could be recognized as an early intervention and a combining therapeutic agent to suppress inflammatory response and scarring formation [90]. The experimental results from other studies further confirmed the above conclusions [91–93]. Tang et al found that in vitro Rg3 prevented the proliferation of keloid fibroblasts, angiogenesis, and collagen synthesis through regulating TGF-β1/Smads and ERK pathways [94]. Furthermore, Tark and co-workers identified protective action of Rb1 on HS [95]. In a word, these findings suggest ginsenosides treatment be a potential strategy regulating skin fibroblasts proliferation. Moreover, another two independent studies revealed the inhibitory action of PNS on oral submucous fibrosis induced by areca nut extract [96] and the inhibitory action of Rg3 on endometriosis [97].

3. Adverse effects

In most cases, no significant side effects have been found in the supplementation with ginseng or ginsenosides. However, mastalgias and vaginal bleeding have been reported by some female patients [98–100]. Because of its estrogen-like effect, ginseng should be applied with extreme caution in women taking progestogens for the possible worsening of side effects of the latter [98]. Subjects treated with warfarin or other anticoagulants or antiplatelet drugs should avoid taking of ginseng-based supplements because of the high risk of bleedings [101]. Subjects receiving digoxin or corticosteroids should also be cautious when taking ginseng [102]. Moreover, in patients taking high doses of Panax ginseng (more than 2.5 g/day), central nervous system effects have been reported, such as insomnia [101,103], tachyarhythmias [99], hypertension [104] and nervousness [101,105]. Other reported side effects of Panax ginseng are gastrointestinal disorders and headaches [101].

4. Limitations and future perspectives

Ginsenosides as natural remedies have been broadly approved to exert therapeutic effects regardless of being used alone or in combination with other drugs in various fibrosis-related in vivo animal models and in vitro cells. However, obstacles must be resolved before ginsenosides therapy can reach clinical application. One of the most difficult impediments is lack of well-designed, randomized, placebo-controlled clinical trials for ginsenosides in humans because of their low bioavailability, such as poor water solubility and biomembrane permeability, instability in gastrointestinal tract, and high metabolic rate in the body. The oral bioavailability is a combined effect of numerous body barriers, preparations, and molecular properties. It has been demonstrated that the majority of ginsenosides had low oral bioavailability [106]. When summarizing the factors that have an impact on oral bioavailability, there are the following four remarkable points. The first is regarding the properties of the compounds. Ginsenosides, as a class of natural glycoside compounds, usually have a large
molecular weight. It is well known that the smaller the molecular weight, the faster the molecular transport through the biofilm, and therefore ginsenosides tend to be absorbed slowly or even incompletely [107]. The second point is the stability of ginsenosides in the gastrointestinal tract. Most of the ginsenosides are easy to degrade or bio-transform under gastric acid and/or intestinal flora conditions, for which they often exert low oral bioavailability [108].

Third, it is associated with membrane permeability. It is widely believed that the higher the permeability, the better the absorption of compounds. Some ginsenosides have poor oral bioavailability because of their limited permeability of intestinal epithelial cell [109,110], and the membrane permeability relates to molecular weight of compounds ability to form hydrogen bond and lipophilicity [111]. Fourth is the diversity of ginsenosides in intestinal and hepatic first-pass effect. Compounds/drugs that enter the portal vein can be effectively metabolized in the gastrointestinal tract and liver, especially during the first-pass process after absorption, which leads to a decrease of bioavailability [112]. Generally, large molecular weight, low water-solubility, and poor gastrointestinal stability of ginsenosides lead to a significant intestinal and hepatic first-pass effect, then leading to low oral bioavailability. Thus, many efforts have been made on figuring out these issues by building effective drug delivery systems and all sorts of administration routes to enhance the bioavailability of ginsenosides, including fibrous membranes [89], vesicles [113], microsphere delivery systems [61], micelles [114], emulsion delivery systems [115], nanoparticle drug delivery systems [116], and so on. These drug delivery systems will greatly enhance the bioavailability of ginsenosides and are capable to slow down, control, release, or target.

Safety is another issue that needs attention. Because the biological function of most natural products is entirely by identifying their pharmacologically active ingredients, unlike the traditional use as an extract or a combination, it is difficult to ensure safety. Solving these problems requires a lot of work. However, it is worth focusing on the intake of ginseng products by subjects receiving cardiac, antidepressant, and anti-hemorrhagic medications for possible side effects.

Evidence that ginsenosides have significant effects on both cancer treatment and tissue fibrosis is accumulating. These two processes share common biological programs, including the occurrence of inflammation and oxidative stress. Ginsenosides have shown an obvious curative effect on these pathophysiological phenomena, indicating that ginsenosides could be a common treatment of cancer and fibrosis by directing inflammation and oxidative stress. Interestingly, ginsenosides can specifically kill tumor cells and inhibit tumor cell proliferation during cancer treatment; meanwhile ginsenosides are also able to promote tumor metastasis by inhibiting the secretion of MMPs and interfering with matrix remodeling [14]. However, during the treatment of fibrotic diseases, ginsenosides conversely exhibit specific killing of activated myofibroblasts and promote the degradation of ECM through up-regulating the expression of MMPs, as well as effectively protect the parenchymal cells of the organ, which is completely different from the molecular mechanism of treating tumors. It still remains unclear how these different effects of ginsenosides can be induced based on cell types or disease environments. The knowledge pertaining the involved detailed deep mechanisms is sparse, although the functional effects of ginsenosides are well established, particularly regarding ginsenosides involvement in anti-fibrosis. More specific mechanisms of ginsenosides (not limited to signaling pathways) require future further evaluation.

Moreover, ginsenosides present diverse actions, such as anti-oxidative, anti-inflammatory, pro-apoptotic, and immunostimulatory performances, with different molecular mechanisms. With this said, it is often hard to standardize the studies because of the diversity of ginsenosides. The different species, cell type, primary or cultivated, harvest time, and methods of processing could affect the pharmacological effects of ginsenosides, so it will be required to investigate the impact of these variables. Additionally, more indepth research using a single preparation should explore the detailed cellular and molecular mechanisms of action, the relationship between structure and function, specificity, toxicity, and pharmacokinetics profile in animal models and humans. It is useful for high-throughput expression array to explore the molecular actions of the various ginsenosides and how the different molecular signaling pathways work together. Furthermore, more explorations are needed to investigate whether synthetic or engineered natural ginsenosides can be used as potential candidates for the treatment of fibrotic diseases, especially if they have better bioavailability, efficacy, safety, and affordability. However, these treatments require further investigation through additional animal experiments and large-scale clinical studies. Upcoming studies will greatly improve the therapeutic potential of ginsenosides, consequently further contributing to the promotion of global health.

5. Conclusions

In this review, we make a brief summary on various types of animal studies concerning human diseases that show similar pathological mechanisms, including chronic inflammation and organ fibrosis. Several important phases involved in the pathological process of tissue fibrosis have been identified, all of which may be affected by ginsenosides. As an advantage to anti-fibrosis, ginsenosides are capable to i) alleviate the activation and proliferation of fibrogenic effector cells (generally refer to myofibroblasts); ii) inhibit the excessive accumulation of ECM, including collagen and fibronectin; iii) reduce oxidative stress and inflammation response, as well as fibrotic markers, especially TGF-β1; and iv) decrease the damage to parenchymal cells, including apoptotic and necrotic changes (Fig. 2). Ginsenosides exert their anti-fibrosis effects in numerous organs, including liver, heart, kidney, lung, and others (Fig. 3). Collectively, ginsenosides attenuate excessive accumulation of ECM and fibrosis in multiple organs.

Tissue fibrosis leads to organ dysfunction, and no effective therapeutics is currently available for this situation. For this reason, anti-fibrotic drugs need to be urgently developed for increasing both quality of life and survival rate of patients with fibrosis and related conditions. Abundant studies have repetitively revealed the therapeutic potential of ginsenosides in animal models of fibrosis-associated human diseases. However, to generate more therapeutic options, more continued work are worth taking into account to clarify the unconfirmed chemical composition and regulatory mechanisms, conduct standard clinical trials, and evaluate the possible side effects. Meanwhile, new guidelines about ginseng usage are required to guarantee safety and effectiveness, which is crucial for preserving the heritage and medical knowledge of our ancestors. The research progress and views provided in this review will be helpful for future exploration of ginsenosides in the development of fibrotic-related diseases therapy and to gain more reliable and reproducible data.

Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data provided for this article can be found online at [https://doi.org/10.1016/j.jgr.2019.12.003](https://doi.org/10.1016/j.jgr.2019.12.003).

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