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REVIEW

Advances in Selenium and Related Compounds Inhibiting Multi-Organ Fibrosis

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Abstract: Selenium (Se), a critically essential trace element, plays a crucial role in diverse physiological processes within the human body, such as oxidative stress response, inflammation regulation, apoptosis, and lipid metabolism. Organ fibrosis, a pathological condition caused by various factors, has become a significant global health issue. Numerous studies have demonstrated the substantial impact of Se on fibrotic diseases. This review delves into the latest research advancements in Se and Se-related biological agents for alleviating fibrosis in the heart, liver, lungs, and kidneys, detailing their mechanisms of action within fibrotic pathways. Additionally, the article summa-rizes some of the anti-fibrotic drugs currently in clinical trials for the aforementioned organ fibroses.

Keywords: selenium, fibrosis, organ, clinical

Introduction

Se, a vital trace element for mammals, has a recommended daily intake ranging from a minimum of 55 μg to a maximum of 400 μg to maintain normal metabolism.[1] Se intake varies worldwide, with some regions in China experiencing both deficiencies and excesses.[2–4] Both Se deficiency and excess can lead to various diseases. Insufficient Se levels can elevate the risk of infections, cancers, cardiovascular diseases, neurological conditions, and other illnesses.[5] Notable diseases associated with Se deficiency Keshan disease[6] and Kashin-Beck disease.[7] Excessive Se consumption can result in Se poisoning, which has been documented in regions such as Enshi, China,[4,8] California,[9] Colorado[10,11] among others in the United States.[11] Symptoms of Se poisoning typically include vomiting, abdominal pain, and heart discomfort, with severe cases potentially leading to death.[12] There is existing evidence associating Se with various disorders, and multiple Se formulations are currently being evaluated in clinical studies. A summary of the clinical findings can be found in Table 1.

Table 1 Selenium and Disease Clinical Trials*

Conditions	NCT Number	Study Status	Phases	Date	Interventions	Sponsor
Liver cirrhosis	NCT00212186	Completed	NA	1998–2024	Se	Vanderbilt University
	NCT01650181	Completed	4	2024–2024	SeMet	Instituto Nacional de Ciencias Medicas Nutricion Salvador Zubiran
	NCT00271245	Terminated	NA	2024–2024	Selenate	Vanderbilt University
Graves'	NCT01247077	Completed	2	2024–2024	Se	Karolinska Institutet
hyperthyroidism	NCT01611896	Unknown	NA	2024–2024	Se	Rigshospitalet, Denmark
Autoimmune	NCT02644707	Completed	4	2024–2024	SeMet	Aristotle University Of Thessaloniki
thyroiditis	NCT02013479	Completed	NA	2023–2023	Selenate	Steen Bonnema

(*Continued*)

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Table 1 (Continued).

Conditions	NCT Number	Study Status	Phases	Date	Interventions	Sponsor
Thyroid ophthalmopathies	NCT03891043	Completed	NA	2024–2024	Se	Instituto de Oftalmologa Fundacin Conde de Valenciana
	NCT02112643	Withdrawn	3	2024–2026	Selenate	Columbia University
Oxidative stress	NCT01150786	Completed	3	2024–2024	Se	Maryam ekramzadeh
	NCT01112449	Completed	NA	2024–2024	Se yeast	Milton S. Hershey Medical Center
COPD	NCT00186706	Completed	4	2024–2024	Se	St. Joseph's Health Care London
	NCT00063453	Completed	3	2024–2024	Se	Cornell University
Prostate cancer	NCT00006392	Completed	3	2024–2024	Se	SWOG Cancer Research Network
	NCT00736645	Completed	2	2024–2024	SeMet	Roswell Park Cancer Institute
	NCT01497431	Completed	I	2024–2024	SeCys	National Cancer Institute
	NCT00978718	Completed	3	2024–2024	Se yeast	University of Arizona
Colorectal cancer	NCT00706121	Completed	3	2024–2024	Se	SWOG Cancer Research Network
	NCT00625183	Terminated	2	2024–2024	SeMet	Roswell Park Cancer Institute
Adult solid tumor	NCT00547547	Completed	I	2024–2024	Se	City of Hope Medical Center
	NCT00112892	completed	I	2024–2024	Se	Roswell Park Cancer Institute
Inflammation	NCT01289925	Terminated	NA	2024–2024	Se	Johns Hopkins University
	NCT01147354	Completed	3	2024–2024	Se yeast	Zahra Sohrabi

Note: *For more information on selenium and disease clinical trials, please refer to the supplementary materials Table S1.

For more information on Se and disease-related clinical trials, please refer to the supplementary materials, specifically Table S1. Tissue fibrosis, a common complication in various diseases, is a leading cause of disability and mortality worldwide.[13] In the United States, approximately 35% of all deaths are attributed to tissue fibrosis.[14] It plays an important role in the occurrence and development of major organ diseases in the human body. Common organ fibroproliferative diseases include liver fibrosis,[15,16] pulmonary fibrosis,[17] myocardial fibrosis,[18] kidney fibrosis,[19] pancreatic fibrosis,[20] splenic fibroplasia,[21] diabetic retinal fibroplasia,[22] myelofibrosis,[23] and nervous system fibrosis.[24] Notably, the heart, liver, lungs, and kidneys are crucial organs, and fibrosis in them directly affects patients' quality of life and lifespan. At present, Se and its related biological agents have been closely associated with fibrotic diseases. This review explores the complex relationship between Se and fibrosis in the liver, heart, lungs, and kidneys, outlining mechanisms in Figure 1 and recent developments in Se-based fibrosis treatments.

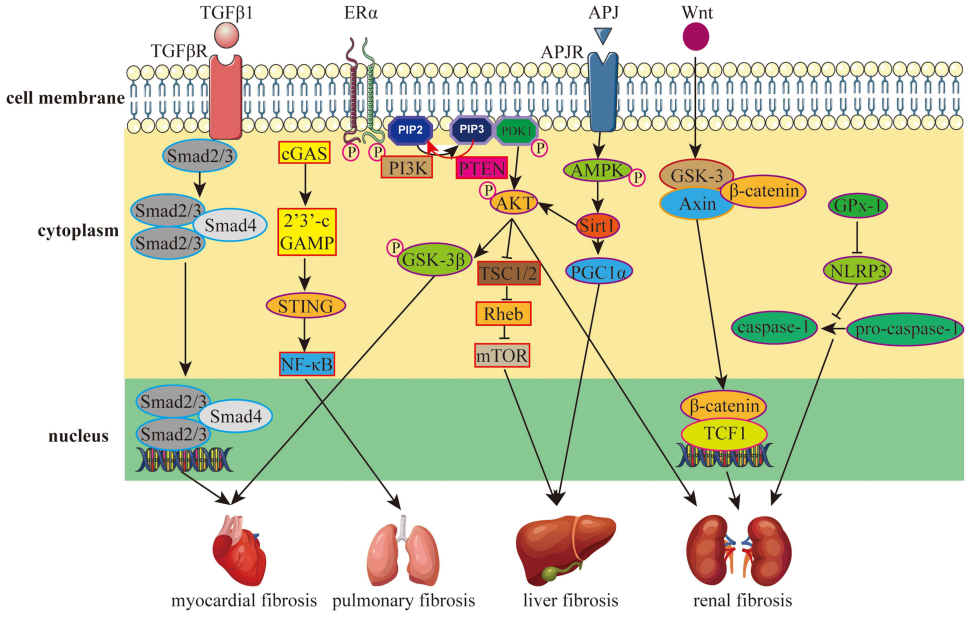

Figure 1 Summary of the mechanism of Se and fibrosis in various organs.

Selenium and Organ Fibrosis Diseases

As one of the trace elements, Se plays a variety of biological roles in the body. The primary biologically active form of Se is selenocysteine (Sec), while selenoproteins represent the main functional forms of Se within organisms.[25] As one of the trace elements, Se plays a variety of biological roles in the body. The primary biologically active form of Se is Sec, while selenoproteins represent the main functional forms of Se within organisms. A total of 25 selenoproteins have been identified in the human body, which can be categorized into six primary groups: the glutathione peroxidase family (GPX), thioredoxin reductase (TrxR), selenoprotein P (SelP), selenoprotein N (SelN), iodothyronine deiodinases (DIO), and selenoprotein R (SelR). A summary of their antioxidant functions is presented in Table 2. The antioxidant effects of selenoproteins may be closely linked to multiple signaling pathways involved in the process of fibrosis. For instance, GPX1 overexpression lowers the levels of reactive oxygen species (ROS), inhibits the protein kinase B (AKT) pathway, promotes apoptosis, and reduces cisplatin resistance in non-small cell lung cancer.[26] GPX2 is regulated by Wnt signaling,[27,28] while the absence of GPX3 activates the NOX4 and protein kinase Cα (PKCα)/mitogen-activated protein kinases (MAPK)/signal transducer and activator of transcription 3 (STAT3) pathways, promoting renal fibrosis.[29] GPx4 knockdown boosts transforming growth factor-β (TGF-β)-induced Smad22/3 signaling, accelerating myofibroblast differentiation.[30] Additionally, TrxR/Trx inhibitors have the potential to mitigate pulmonary fibrosis through the inhibition of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)/TGF-β1/Smads signaling pathway.[31] Fibrosis is a physiological response of the body aimed at counteracting external injury.[13] Following minor damage, fibroblasts are activated and stimulated to proliferate. These cells migrate to the injured area and secrete extracellular matrix (ECM) components, including collagen and fibronectin (FN), which contribute to the formation of granulation tissue.[32] This process establishes a temporary supportive structure for the wound, facilitating cell migration and repair. In the context of wound healing, various growth factors, such as fibroblast growth factor (FGF) and the platelet-derived growth factor (PDGF), activate fibroblasts and other mesenchymal cells, prompting their differentiation into myofibroblasts. This differentiation subsequently remodels the ECM environment to facilitate wound repair. Typically, following wound healing, the ECM is efficiently degraded.[33,34] However, in cases of severe or persistent injury, there can be an over-accumulation of ECM, which leads to necrosis of parenchymal cells, proliferation of connective tissue, and ultimately fibrosis.[35] This complex pathological process involves not only the activation of fibroblasts but also the interplay of multiple signaling pathways. TGF-β is extensively acknowledged as the quintessential pro-fibrotic growth factor implicated in tissue fibrosis.[36] In its latent form, TGF-β, once activated, engages with the heterodimeric TGF-β receptors I (TβR-I) and TβR-II present on the surface of target cells, thereby initiating a series of pro-fibrotic responses via both canonical and non-canonical signaling pathways. The canonical TGF-β signaling pathway entails the phosphorylation of Smad2 and Smad3, which subsequently associate with Smad4 and translocate to the nucleus, where they

Table 2 Main Selenoproteins and Their Antioxidant Functions

Name	Function
Glutathione Peroxidases (GPX1, GPX2, GPX3, GPX4)	The Sec residue is located in the N-terminal region, catalyze the reduction of hydrogen peroxide, lipid peroxides, and organic peroxides in the cytoplasm, cell membrane, and extracellular space by GSH
Thioredoxin Reductases (TrxR1, TrxR2, TrxR3)	The Sec residue is located in the C-terminal region, utilize NADPH as an electron donor to reduce oxidized thioredoxin back to its active form
Iodothyronine Deiodinases (DIO1, DIO2, DIO3)	The Sec residue is located in the C-terminal region, catalyze the conversion of thyroid hormones
Selenoprotein R(SelR)	Utilizes its Sec residue to reduce methionine sulfoxide (MetO) back to methionine, distributed in both the cytoplasm and the nucleus of the cell
Selenoprotein P(SelP)	With an N-terminal redox Sec and multiple C-terminal Sec residues, plasma selenium transport protein
Selenoprotein N(SelN)	Endoplasmic reticulum-resident protein, affect muscle formation and calcium homeostasis regulation

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regulate the transcription of genes associated with fibrosis.[37] Non-canonical TGF-β signaling involves several distinct pathways, notably the MAPK, phosphatidylinositol 3-kinase (PI3K), and Rho Family of Small GTP-Binding Proteins (Rho GTPase) signaling pathways.[38] Beyond TGF-β, various tissue factors, including the PDGF, the FGF, the connective tissue growth factor (CTGF), and the Wnt1, also mediate their effects through the activation of downstream signaling pathways. These pathways encompass RAS/MAPK, PI3K/AKT, JAK/STAT, PI3K/AKT/mammalian target of rapamycin (mTOR), and the Wnt/β-catenin pathway. Significantly, the Wnt signaling pathway, especially its canonical route involving β-catenin, is integral to the processes of wound healing and tissue fibrosis.[39–41] Moreover, the Hippo signaling pathway is integral to the activation of fibroblasts and the synthesis of ECM. Cells detect ECM tension via integrin receptors, which subsequently activate the Hippo pathway. This activation leads to the initiation of downstream effectors Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ), facilitating the cellular response to mechanical cues.[42] Organ fibrosis shares common pathological mechanisms, such as the abnormal deposition of ECM, the activation and proliferation of fibroblasts, and the activation of signaling pathways including TGF-β, Wnt, and Hippo.

However, due to the differences in structure and microenvironment among various organs, there are also differences in the mechanisms.

Myocardial Fibrosis

In recent years, the morbidity and mortality of cardiovascular diseases remain high. One of the common cardiovascular diseases is myocardial fibrosis, which is caused by age, chronic heart disease, myocardial infarction, hypertension, arrhythmia and myocarditis.[43] The principal pathogenesis of myocardial fibrosis is characterized by the proliferation and differentiation of cardiac fibroblasts (cFBs) into myofibroblasts in response to pathological stimuli. This process results in the excessive secretion of extracellular matrix (ECM) components and collagen deposition.[18] Specifically, collagen types I and III are predominant, as they represent the major constituents of the myocardial interstitium. Myocardial fibrosis can be classified into two types: replacement and diffuse myocardial fibrosis. Both types are mediated by cFBs and MFCs. Replacement fibrosis or scar formation is a key process in preventing ventricular wall rupture after ischemic injury. It is induced by cardiomyocyte necrosis resulting from prolonged ischemia, thereby inducing myocardial replacement by fibrous tissue. In contrast, diffuse fibrosis refers to the expansion of interstitial and perivascular spaces without significant loss of cardiomyocytes. This usually occurs in pressure or volume overload, transient repetitive ischemia, aging and cardiomyopathy.[18,44]

During myocardial fibrosis, the activation of the renin-angiotensin-aldosterone system (RAAS) assumes a critical role, distinguishing it from fibrotic processes in other organs. Angiotensin II (Ang II) primarily activates the TGF-β1/Smads signaling pathway through its Type 1 receptors (AT1 receptors), thereby promoting the differentiation of cFBs into myofibroblasts.[45] In contrast, the interaction of Ang II with Type 2 receptors (AT2 receptors) typically exerts inhibitory effects on fibrosis, with AT2 receptors serving as a counter-regulatory mechanism.[46] Furthermore, Angiotensin II (Ang II) has been shown to upregulate the expression of profibrotic mediators, including CTGF and matrix metalloproteinases (MMPs), thereby facilitating ECM deposition and tissue remodeling.[47] Additionally, Ang II significantly influences the activation of cardiac fibroblasts and the recruitment of fibrocyte precursor cells by modulating the inflammatory microenvironment.[48]

It was demonstrated that Se and Se compounds play a pivotal role in the resistance to myocardial fibrosis.[45,46] It has been demonstrated that Se supplementation can increase the activity of GPX and TrxR, thereby improving myocardial ischemia-reperfusion injury and myocardial fibrosis.[49] Moreover, the combination of Se, N-acetyl cysteine, and ascorbic acid has the potential to modify mitochondrial gene expression, which may subsequently lead to an imbalance in the redox system, ultimately contributing to the alleviation of diabetic cardiomyopathy.[50] Concurrently, the provision of Se as a cofactor also regulates the gene expression of related selenoproteins. For instance, as a highly conserved 43 kDa tRNA binding protein, the expression of transfer RNA Sec 1 associated protein 1 (Trnau1ap) was found to beupregulated, accompanied by an increase in the mRNA expression levels of Glutathione, TrxR, and selenoprotein K.[51] Targeted deletion of the SeCys tRNA gene trsp in mice resulted in severe myocarditis and rapid death.[52] It is well known that Se deficiency is associated with Keshan disease. A diet low in Se and vitamin E activates NFκB and increases TGFβ-1 and

CTGF levels, leading to oxidative stress and the induction of the disease.[53,54] Supplementation of trace elements such as zinc, Se and chromium in the offspring of rats with gestational diabetes mellitus (GDM) showed that Se supplementation significantly reduced the activity of cardiac injury markers such as creatine kinase isoenzyme MB (CK-MB) and lactate dehydrogenase (LDH) in GDM offspring rats, and down-regulated maternal GDM-induced expression of fibrosis-related proteins and TGF-β1/Smad3 signaling pathway in the heart tissue of offspring ($P < 0.05$).[55] At the same time, Se can also alleviate cardiac remodeling and delay the progression of myocardial fibrosis and heart failure by regulating the silent information regulator 1 (SIRT1) and AKT/glycogen synthase kinase 3 beta (GSK-3β) pathways.[56] In addition, Se deficiency can also induce myocardial pathological damage and fibrosis abnormalities by activating caspase-9 and caspase-3 in Gpx-1P198L overexpressing transgenic mice.[57]

More and more scholars have developed new anti-fibrosis materials using Se. For example, Sun et al[50] developed a novel self-sustaining Se-embedded nanoparticles (SSSe NPs) that can eliminate multiple reactive ROS to maintain mitochondrial function in the myocardium, thereby effectively reducing cardiomyocyte apoptosis and ferroptosis. More importantly, SSSe NPs have a unique self-sustaining antioxidant effect, which can release Se for GPX4 biosynthesis to promote the repair of endogenous antioxidant system, play a continuous role in clearing ROS, and effectively eliminate inflammation and fibrosis at the site of myocardial infarction. At the same time, SSSe NPs can also effectively induce the production of vascular endothelial growth factor (VEGF) in myocardial infarction tissues, promote vascular repair, and restore myocardial infarction blood flow. Targeted Au-Se core-shell nanostructures (AS-I/S NCs) were found to ameliorate myocardial infarction/reperfusion (MI/RI) injury in rats. This effect is attributed to the inhibition of ROS mediated oxidative damage and the modulation of MAPK and PI3K/AKT signaling pathways.[59] A novel thermosensitive Se-containing polymer hydrogel, namely poly DH-Ss/PEG/PPG urethane (Se-PEG-PPG), can reduce the expression of IL-6 to inhibit inflammation, downregulate the expression of fibrosis-related proteins in vivo to inhibit fibrosis, and improve left ventricular remodeling.[60]

Liver Fibrosis

Liver fibrosis is a pathological process of chronic hepatic parenchymal injury, inflammation, and oxidative stress caused by hepatitis virus infection, alcohol abuse, immune response, drugs, and chemical toxicants, which ultimately leads to abnormal hyperplasia of hepatic fibrous connective tissue.[16,61,62] A 2024 review and meta-analysis found global prevalence rates of advanced liver fibrosis and cirrhosis at 3.3% and 1.3%, respectively, with an increasing trend since 2016.[63] The fundamental process underlying liver fibrosis is characterized by the activation of hepatic stellate cells (HSCs), which secrete ECM components, thereby contributing to both the development of liver fibrosis and the remodeling of liver architecture.[15] There are specific mechanisms and signaling pathways involved in this process. Hepatic macrophages, encompassing Kupffer cells and monocyte-derived macrophages, exhibit a dual function in both the progression and resolution of liver fibrosis. Kupffer cells can polarize into M1 or M2 phenotypes, with the former promoting hepatic inflammatory responses[64] and the latter inhibiting inflammatory reactions and accelerating tissue repair.[65] Macrophage M1 and M2 phenotypes exhibit dynamic plasticity in response to various microenvironmental signals. Histidine-rich glycoprotein (HRG), an endogenous molecular factor, facilitates the polarization of hepatic macrophages towards the M1 phenotype.[66] Similarly, the AC73 and siUSP1 dual drug-loaded lipid nanoparticle, designed to carry milk fat globule epidermal growth factor 8 (MFG-E8) and named MUA/Y, has been shown to promote the transition of macrophages from the M1 phenotype to the M2 phenotype.[67] Sinusoidal capillarization has been implicated in the progression of liver fibrosis. This phenomenon, first introduced by Schaffner,[68] describes the gradual reduction or complete loss of fenestrations in hepatic sinusoidal endothelial cells, accompanied by the formation of a basement membrane beneath the endothelium, leading to a structure that resembles continuous capillaries. Subsequent investigations have demonstrated that hepatic sinusoidal capillarization modifies the liver's microenvironment, influencing both liver hemodynamics and metabolism, which in turn contributes to the development of liver fibrosis.[69] Further analysis has revealed that these changes may be mediated by the leukocyte cell-derived chemotaxin 2 (LECT2)/Tie1 signaling pathway.[70]

Studies have found that Se is associated with a variety of liver diseases such as non-alcoholic fatty liver disease (NAFLD),[70,71] chronic active hepatitis,[72] cirrhosis,[73] liver cancer,[74] prognosis of liver transplantation,[75] and liver

fibrosis.[64] Epidemiological studies have demonstrated that low serum Se is closely related to liver fibrosis.[76–79] Regression analysis further showed that serum in serum (S-Se) was positively correlated with serum albumin and plasma FN, while S-Se was negatively correlated with the amino terminal peptide of type III procollagen (NPIIIP).[80] Low Se levels drive higher expressions of metalloproteinases (MMP1/3) and their tissue inhibitors of metalloproteinases (TIMP1/3).[81] On the contrary, the expression and activity of GPX and superoxide dismutase(SOD) increased, while the levels of malondialdehyde (MDA), tumour necrosis factor-α (TNF-α), IL-6 and monocyte chemotactic protein-1 (MCP-1) decreased under high Se levels.[82] In CCl4-induced liver fibrosis, high Se level increase the apoptosis level of HSCs, upregulate the expression of TIMP-1 and inhibit the activity of HSCs. Additionally, they downregulate the signal transduction of silent information regulator 1 (SIRT1) and MAPK, subsequently decreasing the expression of collagen, TGF-β and hydroxyproline.[82–84]

Other forms of Se are also closely related to liver fibrosis. H_2Se leads to the degradation of collagen IV by decoupling the thiamine bond and reduces the remodeling of ECM.[85] Selenite reduces the number of activated HSCs, attenuates the stimulating effect of TGFβ1, reduces the production of collagen 1 and IL-8, and increases the expression of matrix metalloproteinase-9 (MMP-9).[86,87] Short-term Se deficiency dietary intervention could lead to liver fibrosis by AKT mTOR signaling pathway.[88] Dietary Se, zinc and allopurinol supplements can stabilize the liver ultrastructure through antioxidant reduction, thereby improving the disturbance of blood and liver manganese levels in rats.[89] In addition, supplementing with adequate amounts of vitamin E and Se can reduce the accumulation of type I collagen mediated by TGFβ1 and inhibit the activation and proliferation of HSCs induced by CCl4, as well as promote apoptosis of activated HSCs during the acute injury phase.[83,90,91] The combination of anti-fibrotic herbs and Se can prevent fibrosis by boosting immunity and inhibiting the expression (NF-κB) and TGF-β1.[92] Butaselen (BS), a new inhibitor of Se-containing TrxR, inhibits the activation of HSCs by blocking the TGF-β1/Smads pathway, thereby preventing the production of α-smooth muscle actin (α-SMA) and collagen.[93] Selenium nanoparticles (SeNPs) downregulate pro-fibrosis and pro-inflammation genes, downregulate the expression of unc-51 like autophagy activating kinase 1 (ULK1) and phosphorylated ULK1 protein as well as mitochondrial autophagy levels, and up-regulate the expression of mTOR and phosphorylation-modified mTOR proteins, thus reducing the severity of liver pathological injury and fibrosis.[94] SeNPs also have been shown to alleviate liver fibrosis induced by thioacetamide (TAA) through the induction of endoplasmic reticulum (ER) stress, activation of the protein kinase R-like endoplasmic reticulum kinase (PERK) signaling pathway, and initiation of an adaptive unfolded protein response (UPR).[95] Accordingly, the elimination of inflammation and resistance to oxidative stress may be potential mechanisms by which high Se levels reduce liver fibrosis.

It has been found that organic Se-rich products play an important role in anti-fibrosis. The novel Se-enriched probiotics (SP) significantly decreased the expression of α-SMA, collagen, TGF-β1, TIMP-1 and inflammation-related genes in CCl4-treated rats, and induced apoptosis of activated HSCs.[82] The mechanism may be to activate SIRT1 signal and weaken liver oxidative stress, ER stress, inflammation and MAPK signal transduction.[84] In vivo hepatotoxicity models have demonstrated that nano-Se can exert an antagonistic effect on cadmium-induced hepatocyte pyroptosis by targeting the APJ-AMPK-PGC1α pathway.[96] Further studies have found that SP can also reduce liver oxidative damage after high ambient temperature treatment in rats.[97] Compared with supplementing Se-enriched yeast (SY) alone, the combination of SY and gum arabic (GA) can significantly improve the expression of collagen 1, α-SMA and TGFβ1, significantly inhibit inflammation, and play an anti-fibrotic role.[98] Compared with ordinary green tea, Se-rich green tea plays an important role in improving liver ECM deposition and scarring, as well as 5-hydroxytryptamine (5-HT) and 5-HT receptor (5-HTR) 2A/2B signal transduction.[99]

Pulmonary Fibrosis

Pulmonary fibrosis is a chronic and fatal lung disease, primarily induced by viral infections, drugs, autoimmune diseases, connective tissue disorders, antigenic hypersensitivity or pulmonary sarcoidosis.[100] The main pathological features include heterogeneous fibrosis, fibroblast foci, disordered collagen and excessive deposition of ECM, resulting in the loss of normal lung structure, with or without honeycomb cyst formation, which has a significant impact on the global population aging.[17,100] Coronavirus disease (COVID-19) was first reported in Wuhan, China at the end of 2019.[91] So far, the infection has spread to almost all countries around the world. The pathogenesis of COVID-19 includes inhibition of

host antiviral and innate immune responses, induction of oxidative stress, followed by severe inflammation known as "cytokine storms", leading to acute lung injury, pulmonary fibrosis, and pneumonia.[101–104] Studies have shown that a large number of patients with COVID-19 have Se deficiency and high mortality.[105] Moghaddam et al[105] found that appropriate doses of Se can be used as a supportive treatment for COVID-19. Compared with the placebo group, β-glucan rich in Se and zinc and the nutritional supplement of probiotic Saccharomyces cerevisiae (ABBC1) can make the humoral and cellular immune response intensity of COVID-19 higher and enhance immunity.[106] The mechanism may be that selenoprotein can enhance T cell proliferation and NK cell activity, and can also enhance the body's response to vaccines and immunity to pathogens, thereby inhibiting severe inflammation in tissues such as lung and intestine.[107] Therefore, we suspect that one of the possible reasons for the extremely high mortality in COVID-19 patients is that Se deficiency leads to down-regulation of selenoprotein expression, resulting in the inability of selenoproteins to counteract oxidative stress caused by viral infection. At present, several nutritional health products, including Se, have been proved to have the ability to enhance immunity, antiviral, antioxidant and anti-inflammatory effects. Food supplements may help strengthen the immune system, prevent transmission of COVID-19 virus, suppress lung inflammation, and prevent it from progressing to the stage of lung fibrosis.[104]

Studies have shown that Se-Met can provide cellular protection through different mechanisms. On one hand, it regulates the cGAS/STING/NF-κB pathway to inhibit pulmonary inflammatory responses and prevent cellular senescence.[108] On the other hand, it enhances the expression of GPx4 to protect cells from ferroptosis and alleviate ER stress, thereby reducing cellular oxidative stress and ferroptosis. SeNPs not only have the advantages of reducing toxicity, increasing biological activity, promoting cell targeting and improving bioavailability, but also have potential anti-inflammatory and anti-fibrosis effects, regulating the expression of NF-κB, nuclear factor erythroid 2-related factor 2 (Nrf2), redox imbalance and MAPK.[109,110] Furthermore, SeNPs have also been shown to inhibit the activity of TGF-β, which is an ideal feature to prevent the progression of organ fibrosis.[111,112] Yinghua et al[113] constructed a Se-containing metal complex drug delivery system (RuSe), which can reduce inflammation in lung tissue of mice by activating GPX1/TrxR, inhibit apoptosis in lung tissue, and effectively alleviate pulmonary fibrosis.

Renal Fibrosis

In 2017, the worldwide prevalence of chronic kidney disease (CKD) was estimated to be 9.1%.[114] CKD is characterized by persistent abnormalities in kidney structure or function lasting longer than three months, with renal fibrosis serving as a prevalent clinical pathological feature, and ultimate manifestation of the disease.[115] In renal fibrosis, myofibroblasts primarily come from resident interstitial fibroblasts, and most of the ECM is generated by interstitial cells, while only a minor part is derived from dedifferentiated proximal renal tubule cells.[116] In the study of kidney fibrosis, scholars have introduced the novel concept of the fibrogenic niche, which refers to the observation that fibrosis is not uniformly distributed in the renal parenchyma but begins to form in certain local areas, thereby creating a unique tissue microenvironment.[117] The latest research has, for the first time, confirmed that the depletion of GPX3 activates the NOX4/ROS/PKCα/MAPK/STAT3 signaling pathway, leading to oxidative stress in the extracellular microenvironment.[29] This oxidative stress, in turn, drives the activation of fibroblasts and the development of kidney fibrosis. Therefore, strategies targeting this oxidative stress microenvironment may be a new approach for the prevention and treatment of kidney fibrosis in the future. Se prevents renal fibrosis by regulating MMPs and TIMPs in streptozotocin-induced diabetic rats.[29] However, whether Se is directly involved in these regulatory processes associated with renal fibrosis remains unknown. In the study, rats exposed to both T-2 toxin and Se edeficiency experienced a synergistic effect that potentially suppressed the activation of the PI3K/AKT and NF-κB signaling pathways, leading to exacerbated inflammatory responses, promoted EMT, and increased deposition of ECM.[118] As a novel intervention, SeNPs have been found to alleviate fibrosis induced after acute kidney injury (AKI) by modulating the GPx-1/NLRP3/Caspase-1 signaling pathway.[119] We believe that Se deficiency may lead to excessive accumulation of ECM, irregular secretion of MMPs, activation of the Wnt/β-catenin pathway, and alterations in EMT, thereby causing renal fibrosis.

Discussion

As our understanding of abnormal signaling pathways in organ fibrosis improves, the development of anti-fibrotic drugs is advancing steadily. We have summarized some of the drugs that are currently in clinical trials, mainly involving myocardial fibrosis, liver fibrosis, pulmonary fibrosis, and kidney fibrosis, as shown in Tables 3–6. For more clinical randomized controlled trials on myocardial fibrosis, liver fibrosis, pulmonary fibrosis, and renal fibrosis, please refer to the supplementary materials, specifically Tables S2–S4. Because of no obvious clinical manifestations and invasive diagnosis in the early stage of organ fibrosis, the diagnosis is difficult. Clinical imaging techniques, such as computed tomography (CT), ultrasound, and magnetic resonance imaging (MRI), can detect formed fibrosis in the lung, liver, and heart, but are less sensitive in detecting early diseases. In terms of treatment, a few anti-fibrosis treatments alleviate

Table 3 Clinical Trials on Myocardial Fibrosis*

Interventions	NCT Number	Study Status	Phases	Date	Sponsor
Spironolactone	NCT00879060	Completed	4	2007–2011	Tufts Medical Center
	NCT02285920		2	2014–2017	University of Pennsylvania
	NCT00663195		4	2004–2005	Tottori University Hospital
	NCT01069510		4	2010–2016	Oregon Health and Science University
Pirfenidone	NCT02932566	Completed	2	2017–2019	Manchester University NHS Foundation Trust
	NCT00011076	Completed	2	2001–2003	National Heart, Lung, and Blood Institute
	NCT05531955	Not recruiting	2	2022–2024	Shanghai Zhongshan Hospital
Dapagliflozin	NCT03782259	Completed	4	2019–2022	University of Washington
	NCT05848102	Recruiting	4	2022–2024	Sun Yat-sen University
	NCT05420285	Recruiting	2	2022–2023	Assistance Publique - Hpitaux de Paris
	NCT06201000	Recruiting	NA	2023–2024	October 6 University
Enalapril	NCT02432885	Completed	3	2009–2012	InCor Heart Institute
Pycnogenol	NCT00952627	Terminated	2	2009–2010	University of Arizona

Note: *For more information on myocardial fibrosis clinical trials, please refer to the supplementary materials Table S2.

Table 4 Clinical Trials on Liver Fibrosis*

NCT Number	Study Status	Phases	Date	Interventions	Sponsor
NCT02227459	Completed	1	2024–2024	ND-L02-s0201	Bristol-Myers Squibb
NCT00180674	Completed	2	2024–2024	Warfarin	Imperial College London
NCT01935817	Completed	3	2024–2024	Silybin	University of Catania
NCT00043303	Completed	2	2024–2024	IFN γ-1b	InterMune
NCT01938781	Completed	4	2024–2024	Entecavir	Beijing Friendship Hospital
NCT00956098	Completed	2	2024–2024	Oltipraz	HK inno.N Corporation
NCT00347009	Completed	4	2024–2024	Adefovir dipivoxil	GlaxoSmithKline
NCT00049842	Completed	3	2024–2024	peg-IFN α-2b	Merck Sharp & Dohme LLC
NCT00298714	Completed	4	2024–2024	Losartan	Hospital Clinic of Barcelona
NCT02161952	Completed	2	2024–2024	Pirfenidone	University of Guadalajara
NCT01231685	Completed	2	2024–2024	Raltegravir	McGill University Health Centre
NCT03420768	Completed	2	2018–2019	BMS-986263	Bristol-Myers Squibb
NCT03659058	Completed	NA	2016–2018	Silymarin	Zagazig University
NCT02400216	Completed	2	2015–2017	Dual cholate	National Institute of Diabetes and Digestive and Kidney Diseases
NCT01707472	Completed	2	2012–2014	Simtuzumab	Gilead Sciences
NCT00244751	Completed	2	2005–2018	GI262570	GlaxoSmithKline

Note: *For more information on liver fibrosis clinical trials, please refer to the supplementary materials Table S3.

Table 5 Clinical Trials on Pulmonary Fibrosis*

Conditions	NCT Number	Study Status	Phases	Date	Interventions	Sponsor
IPF	NCT03567785	Completed	4	2018–2021	Pirfenidone	KU Leuven
	NCT03710824	Completed	NA	2019–2023	Nintedanib	Boehringer Ingelheim
	NCT01136174	Completed	2	2024- now	BIBF 1120	Boehringer Ingelheim
	NCT04552899	Completed	3	2021–2023	PRM-151	Hoffmann-La Roche
	NCT03981094	Completed	1	2019–2019	BMS-986278	Bristol-Myers Squibb
CF	NCT05274269	Completed	3	2022–2023	Ivacaftor	Vertex Pharmaceuticals Incorporated
	NCT03256968	Completed	4	2017–2018	Ataluren	University of Alabama at Birmingham
	NCT01132482	Completed	2	2015–2017	Sildenafil	National Jewish Health
	NCT00625612	Completed	3	2008–2010	Denufosol tetrasodium	Merck Sharp & Dohme LLC
	NCT02134353	Completed	3	2014–2017	Mannitol	Syntara
PF	NCT04461587	Completed	2	2020–2022	Pirfenidone	Pulmonary Research of Abingdon, LLC
	NCT04308681	Completed	2	2020–2022	BMS-986278	Bristol-Myers Squibb
	NCT04279197	Completed	2	2020–2021	Fuzheng huayu tablet	ShuGuang Hospital
	NCT03559166	Completed	1	2018–2019	bld-2660	Blade Therapeutics
	NCT00000596	Completed	2	1978–1983	Prednisone	National Heart, Lung, and Blood Institute
ILD	NCT03313180	Completed	3	2017–2023	Nintedanib	Boehringer Ingelheim
	NCT02630316	Completed	2/3	2017–2019	Inhaled treprostinil	United Therapeutics
	NCT02370693	Completed	2	2016–2020	Bortezomib	Northwestern University
COVID-19	NCT05648734	Completed	NA	2022–2022	Corticosteroids	Mansoura University
	NCT04551781	Completed	NA	2020–2020	Prednisone	South Valley University

Note: *For more information on pulmonary fibrosis clinical trials, please refer to the supplementary materials Table S4.

Table 6 Clinical Trials on Renal Fibrosis

NCT Number	Study Status	Phases	Date	Interventions	Sponsor
NCT00677092	Completed	2	2024–2024	Imatinib mesylate	Massachusetts General Hospital
NCT01860183	Completed	4	2024–2026	Mycophenolate mofetil	Clinical Hospital Merkur
NCT00865449	Completed	3	2024–2024	Spironolactone	Instituto Nacional de Cardiologia Ignacio Chavez
NCT01359345	Unknown	2,3	2024–2024	Gadolinium	Imam Khomeini Hospital
NCT00493194	Unknown	4	2024–2024	Sirolimu	University Hospital, Antwerp

fibrosis by delaying the rate of fibrosis progression.[120,121] However, due to the slow progression of organ fibrosis disease, which makes clinical trials long and costly, there are great challenges in the diagnosis and treatment of fibrosis.[122]

In recent years, the interplay between Se and human health has garnered significant attention, particularly regarding its integral role in thyroid function. During the synthesis of thyroid hormones, thyroid follicles continuously generate hydrogen peroxide (H_2O_2), necessitating a robust antioxidant system to safeguard cells from damage induced by H_2O_2 and ROS.[123] Se serves as a vital component of various antioxidant enzymes that neutralize free radicals within the body, thereby mitigating oxidative stress and cellular damage. Additionally, deiodinases (DIO) play a crucial role in the synthesis, activation, and metabolism of thyroid hormones, primarily responsible for converting T4 into the more potent T3.[124] Se is an essential component of the deiodinases, thus, a deficiency in Se may impair the activity of these enzymes, subsequently influencing the metabolism of thyroid hormones. Dysregulation of thyroid hormone metabolism, whether resulting in hyperthyroidism or hypothyroidism, can contribute to cardiovascular complications.[125] For instance, an excess of thyroid hormones can elevate heart rate, increase cardiac stress, and induce atrial fibrillation, thereby posing life-threatening risks.[126] Elevated concentrations of FT3 are significantly correlated with an increased risk of coronary artery events,[127] indicating that thyrotoxicosis may contribute to myocardial ischemia and infarction, even without pre-existing coronary artery disease.[128] In a hypothyroidism animal experiment, just 6 weeks of propylthiouracil (PTU)

supplementation was enough to cause a decrease in heart weight, chamber dilation, reduced coronary function, and impaired blood flow.[129]

Furthermore, Se has become a focal point in cancer research.[130] A particularly remarkable study was conducted by the Arizona Cancer Center, which stands out for its significant findings. In this 13-year-long double-blind clinical trial, 1321 cancer patients received a daily supplement of 200 micrograms of selenium. The results demonstrated a 37% reduction in cancer incidence and an impressive 50% decrease in mortality rates.[131] Se's principal anti-neoplastic mechanism involves triggering apoptosis in cancer cells. Se and its compounds have been demonstrated to initiate the apoptotic cascade, with the engagement of caspases being an essential component of this cell death sequence.[132,133] Additionally, selenium nanoparticles can induce autophagy in colorectal cancer cells, indicating that Se influences other forms of cell death beyond apoptosis.[134] The ability of Se to modulate oxidative stress is another critical aspect of its anti-cancer properties. Se compounds can enhance the production of ROS within cancer cells, leading to oxidative damage and subsequent cell death. This may be related to the increased susceptibility of cancer cells to the effects of oxidative stress.[132,135] This may be related to the increased susceptibility of cancer cells to the effects of oxidative stress. Se possesses a variety of complex anticancer mechanisms, which collectively highlight its potential as a cancer therapeutic agent.

In summary, Se and selenium compounds have a significant impact on the pathogenesis and treatment of organ fibrosis diseases, and we should explore how selenium can better treat fibrosis diseases and bring the gospel to patients with fibrosis.

Conclusion

Se and Se-relatedits compounds can interfere with particularly in the occurrenceform of SeC, play a vital role in exerting their antioxidant and development of fibrotic diseases by affecting the redox process and affecting fibrosis-relatedfunctions. By reduc-ing oxidative stress, Se helps to inhibit signaling pathways. A variety of Se compounds can be used associated with fibrosis, such as ideal potential drugs TGF-β, Wnt, and Hippo, thereby reducing the activation and proliferation of myofibroblasts. Consequently, Se may emerge as a significant intervention for the prevention and treatment of fibrosis, which can bring gospel to patients withorgan fibrosis.

Abbreviations

Se, Selenium; selenoproteins, Se-containing proteins; SeCysSec, selenocysteine; SeMet, selenomethionine; cFBcFBs, cardiac fibroblasts; MFC, myofibroblasts; ECM, extracellular matrix; AT1AT1R, Angiotensin II Type 1 Receptor; TGF-β, transforming growth factor-β; TNF-α, tumortumour necrosis factor-α; IL-1, interleukin-1; IL-10, interleukin-10; PDGFsFGF, fibroblast growth factor; CTGF, connective tissue growth factor; PDGF, platelet-derived growth factorsfactor; MDA, malondialdehyde; α-SMA, α-smooth muscle actin; TβR-I, transforming growth factor beta receptorTGF-β receptors I; TβR-II, transforming growth factor beta receptor II; PKCα, protein kinase Cα; STAT3, signal transducer and activator of transcription 3; MAPK, mitogen-activated protein kinasekinases; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; NF-κB, activated B cells; RHO GTPases, ras homology GTPases; GPxRho Family of Small GTP-Binding Proteins; YAP, Yes-associated protein; TAZ, PDZ-binding motif; Ang II, Angiotensin II; GPX, glutathione peroxidase; TrxR, thioredoxin reductase; SOD, superoxide dismutase; GSH, glutathione; Trnau1ap, RNA selenocysteine 1 associated protein 1; GDM, gestational diabetes mellitus; CK-MB, creatine kinase isoenzyme MB; LDH, lactate dehydrogenase; MFG-E8, milk fat globule epidermal growth factor 8; LECT2, leukocyte cell-derived chemotaxin 2; SeNPs, Selenium nanoparticles; SSSe NPs, self–sustaining Se–embedded nanoparticles; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor; AS-I/S NCs, Au-Se core-shell nanostructures; MI/RI, myocardial infarction/reperfusion; SIRT1,silent information regulator 1; AKT, the protein kinase B; GSK-3β, glycogen synthase kinase 3 beta; ROS, reactive oxygen species; Se-PEG-PPG, poly DH-Ss/PEG/PPG urethane; HSCs, hepatic stellate cells; HBV, hepatitis B virus; BDL, bile duct ligation; NAFLD, non-alcoholic fatty liver disease; FN, fibronectin; NPIIIP, amino-terminal peptide of type III procollagen; MMP1/3MMPs, matrix metalloproteinases; TIMP1/3, tissue inhibitors of metalloproteinases; MDA, malondialdehyde; MCP-1, monocyte chemotactic protein-1; SIRT1, silent information regulator 1; MMP-9, matrix metalloproteinase-9; mTOR, mammalian target of rapamycin; BS, Butaselen; ULK1, unc-51

like autophagy activating kinase 1; TAA, thioacetamide; ER, endoplasmic reticulum; PERK, protein kinase R-like endoplasmic reticulum kinase; UPR, unfolded protein response; SP, Se -enriched probiotics; SY, Se-enriched yeast; GA, gum arabic; 5-HT, 5-hydroxytryptamine; 5-HTR, 5-HT receptor; COVID-19, Coronavirus disease; Nrf2, erythroid 2-related factor 2; CKD, chronic kidney disease; EMT, epithelial-mesenchymal transition; HMC, human glomerular mesangial cell; AKI, acute kidney injury; CT, computed tomography; MRI, magnetic resonance imaging.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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