

Effects of Natural Products through Inhibiting Endoplasmic Reticulum Stress on Attenuation of Idiopathic Pulmonary Fibrosis

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Abstract: With ever-increasing intensive studies of idiopathic pulmonary fibrosis (IPF), significant progresses have been made. Endoplasmic reticulum stress (ERS)/unfolded protein reaction (UPR) is associated with the development and progression of IPF, and targeting ERS/UPR may be beneficial in the treatment of IPF. Natural product is a tremendous source of new drug discovery, and accumulating studies have reported that many natural products show potential therapeutic effects for IPF via modulating one or more branches of the ERS signaling pathway. Therefore, this review focuses on critical roles of ERS in IPF development, and summarizes herbal preparations and bioactive compounds which protect against IPF through regulating ERS.

Keywords: idiopathic pulmonary fibrosis, endoplasmic reticulum stress, natural products, mechanisms

Introduction

Idiopathic pulmonary fibrosis (IPF) is an idiopathic interstitial pneumonia featured by progressive dyspnea, exercise intolerance, hypoxemia, and respiratory failure, occurring primarily in older adults.¹ IPF is identified by the presence of patchy areas of fibrotic remodeling in the distal lung parenchyma with fibroblastic foci.^{2,3} Currently, the epidemiological studies of IPF indicated a morbidity of 2–30 cases/100,000 per annum and a prevalence of 10–60 cases/100,000.⁴ What's more, median survival times for suffering from IPF are considered to be from 3 to 5 year.^{5–9} So far, several evidence shows that the progress of IPF is influenced by various factors including environmental factors,¹⁰ gene variants,¹¹ aging alterations,¹² epigenetic reprogramming,¹² and comorbid diseases.¹³ However, the etiology is still unclear, the current perspectives on the etiology of IPF is the appearance of extracellular matrix (ECM) and fibrosis caused by continuous local micro-injuries causing DNA damage, imbalanced cell death and anomalous tissue remodeling.^{4,14–16} Drug development for IPF has been challenging because of poorly understood disease etiology.¹⁷ Consequently, it is in great demand to clarify the pathological mechanisms of IPF, and discovery potential drug candidates.

Previously, IPF believed to be a chronic and sustained inflammatory response process,¹⁸ however, current evidence suggests that the fibrotic process is primarily driven by abnormal activation of alveolar epithelial cells (AECs). The activated AECs can release mediators that facilitate the proliferation of resident mesenchymal cells, attract circulating fibrocytes, and induce the epithelial to mesenchymal transition (EMT),¹⁹ ultimately making for fibrous lesion formation. Consequently, the focus produce excessive much collagen-based ECM, causing scar and lung remodeling.²⁰

The endoplasmic reticulum (ER) as an active intracellular organelle is stemmed from the outer membrane of the nucleus. Under physiological conditions, a cell generates about 4×10^6 proteins every minute, furthermore, the function of the ER is to

preliminary fold and process not less than one-third of those proteins.²¹ The ER not only harmonizes protein fold, process, assemble and transport, but also degrades the misfolded proteins. The factors, for instance, protein load, cell metabolism, redox balance, and calcium homeostasis, can affect the ER function by promoting ER stress (ERS) as well as the adaptive response – unfolded protein reaction (UPR)^{21–25} and cell death.²⁶

Recently, cumulative investigations have disclosed that ERS can promote the progression of many diseases, including depression,²⁷ cardiovascular,^{28,29} neurodegenerative diseases,³⁰ cancer,³¹ obesity, and diabetes.^{32–35} These years, numerous investigations have reported that ERS is closely associated with the development of lung diseases such as silicosis,³⁶ asthma,³⁷ non-small cell lung cancer,³⁸ acute lung injury,³⁹ and IPF.^{40,41} It has been demonstrated that during the progress of IPF, ERS is activated and administration of the ERS inhibitors can alleviate fibroblast proliferation and improve lung function, suggesting an important factor of ERS for the pathogenesis of IPF.^{42,43}

Lately, there has been a growing area of interest in studying natural products for their potential pharmacological activities and mechanisms in treating IPF. All sorts of natural products, for instance, alkaloids, flavonoids, polyphenols, terpenoids, and steroids have been reported to have ability to prevent IPF development owing to inhibiting ERS, inflammatory, apoptotic, and oxidative actions. However, there is currently a lack of comprehensive studies that have summarized the role of natural products in treating IPF through the inhibition of ERS signaling. Therefore, in this article, we underwent a thorough search of databases including PubMed, Web of Science, and CNKI databases for reviews and articles published from 1998 to 2023 (up to June), with search terms (“Pulmonary fibrosis” OR “Lung fibrosis”) AND (“endoplasmic reticulum stress” OR “Unfolded protein reaction”) AND (“bioactive compound” OR “plant extract” OR “herbal preparation”). In summary, this paper concludes the participation of ERS in IPF development, and summarizes the natural products which provide potential benefits in the treatment of IPF through regulating ERS signaling pathway.

Endoplasmic Reticulum Stress and the Unfolded Protein Reaction

As an organelle, the ER is essential to regulate proteostasis, calcium storage, lipid synthesis, and mitochondrial function. Both protein misfolding and subsequent ERS causing the activation of UPR through regulating protein kinase-like endoplasmic reticulum kinase (PERK), activating transcription factor 6 (ATF6), and inositol-requiring enzyme 1 α (IRE1 α), to maintain its membrane-bound state of non-activation or bind to glucose-reactive protein 78 (GRP78). The UPR is activated to cope with the stress reaction; however, serious situation can ultimately lead to cell death. During the process of UPR, amounts of chaperones, for instance, protein disulfide isomerases (PDIs), cyclophilin B, CaBP1 (calcium-binding protein) and stromal Cell Derived Factor 2 Like Protein 1 (SDF2-L1), are upregulated with the purpose of restoring ER homeostasis.^{44,45}

The ATF6 pathway is activated by unfolded/misfolded proteins and separated from the immunoglobulin heavy-chain binding protein (BIP, namely, GRP78 or heat shock 70 kDa protein 5 (HSPA5)). In resting state, BIP remains stably bound to ATF6, but upon activation, the dissociation of BIP initiates a cascade of signaling pathways.⁴⁶ However, the activation of IRE1 and PERK remains unclear, despite the presence of compatible sensing domains that facilitate homodimerize. Three different hypotheses have been proposed to explain this phenomenon: direct recognition, indirect recognition, and the hybrid recognition. Direct recognition is defined as that unfolded proteins activate the sensor IRE1 to trigger the UPR in the ER luminal;⁴⁷ Indirect recognition is defined as that both PERK and IRE1 form a steady complex with BIP;⁴⁸ Hybrid recognition is defined as that BIP dissociation and unfolded protein binding trigger the UPR signaling pathways.^{49–51}

ATF6

Normally, ATF6 remains inactive in its membrane-bound form; however, ATF6 activation results in its free from the ER and move to the Golgi,⁵² where it is divided by site-1 proteases into amino terminal (N-terminal) and carboxy terminal domains, then N-terminal fragment is liberated, subsequently, these both new and smaller proteins are transferred into the nucleus to carry out transcriptional activities.^{53,54} Consequently, several chaperones proteins, including protein disulfide isomerase associated 6 (PDIA6) gene,⁵⁵ calreticulin,⁵⁶ and X-box binding protein 1 (XBP1), are activated by IRE1-XBP1 pathway.^{57,58}

IRE1

IRE1 as a kind of type I transmembrane protein kinases existed in the ER transmits stress signals in answer to unfolded protein, which is the first and the most evolutionarily conserved branch of the UPR.^{59–61} Once ERS are

detected, trans-autophosphorylation and dimerization of IRE1 activate its RNase domain. Although endoribonuclease activity plays a significant part in reducing the amount of proteins entering the ER lumen, and regulating the XBP1mRNA transcript.^{52,62} This splicing causes a change in the C-terminal region of XBP1, and only the XBP1 piece, which is a transcriptional factor in connection with a diversity of UPR target genes,⁶³ including refolding and degrading genes.⁶⁴

PERK

PERK is also a transmembrane endoplasmic reticulum resident protein. Similar to IRE1, PERK also belongs to Type I transmembrane protein. When feeling ERS, PERK is activated, and then homodimerized and auto-phosphorylated.⁶⁵ Subsequently, the alpha subunit of eukaryotic translation Initiation factor 2 α (eIF2 α) at Ser51 is activated and phosphorylated (p-eIF2 α), which causes the suppressant of eIF2 β and suppression of protein synthesis.⁶⁶ Therefore, PERK plays an indispensable role in decreasing ERS through reducing the production of nascent proteins. ATF4 is a key gene for ERS-induced autophagy and apoptosis by activating these proteins,^{67,68} such as C/EBP homologous protein (CHOP),⁶⁹ parkin,⁷⁰ and CD36,⁷¹ et al. The phosphorylated eIF2 α can selectively activate ATF4, resulting in modulating amino acid transport, antioxidant defenses, and the biosynthesis of lipids the transcription factor.^{52,72} Notably, when the ERS persists continuously, autophagy is defined as the last guardian to restore the homeostasis of ER through engulfing the damaged ER⁷³ (Figure 1).

The Effect of Endoplasmic Reticulum Stress in Different Cell Types on Lung Fibrosis

Based on the currently available data, it has been proved that ERS and UPR are related to lung fibrosis via initiating the induction of alveolar epithelial cells (AECs) apoptosis, differentiation of fibroblasts to myofibroblasts, M2 polarization of macrophage, and Th17 cell differentiation^{26,74–77} (Figure 2).

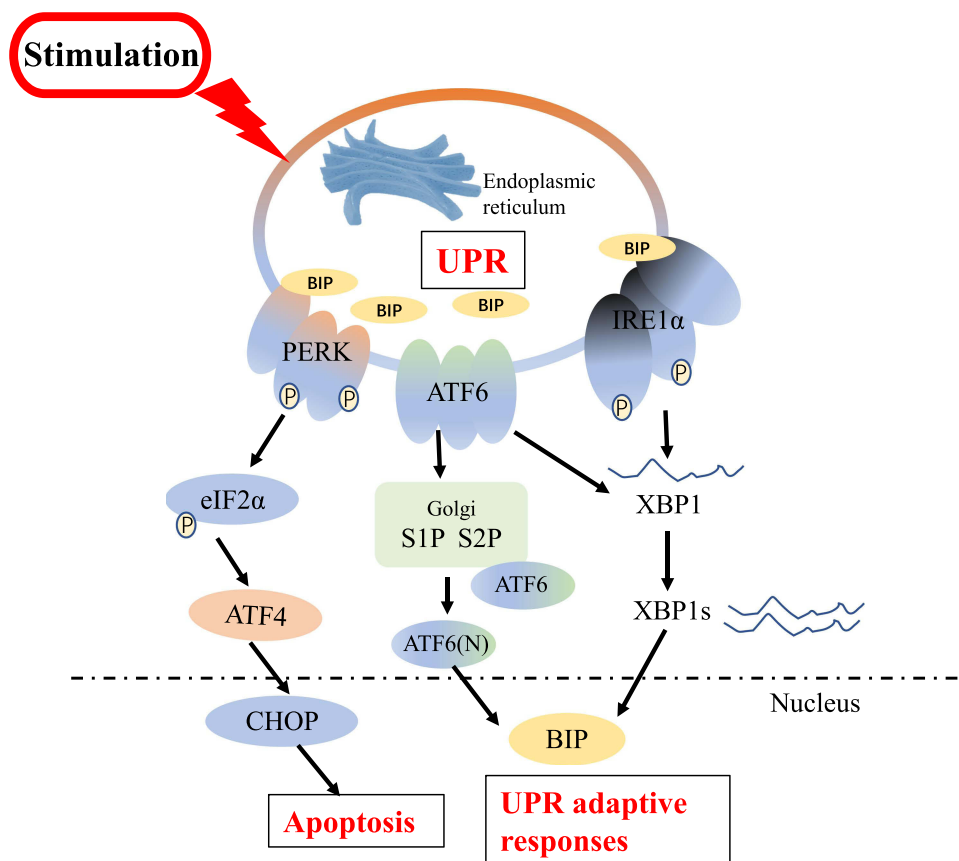


Figure 1 ERS and the UPR.

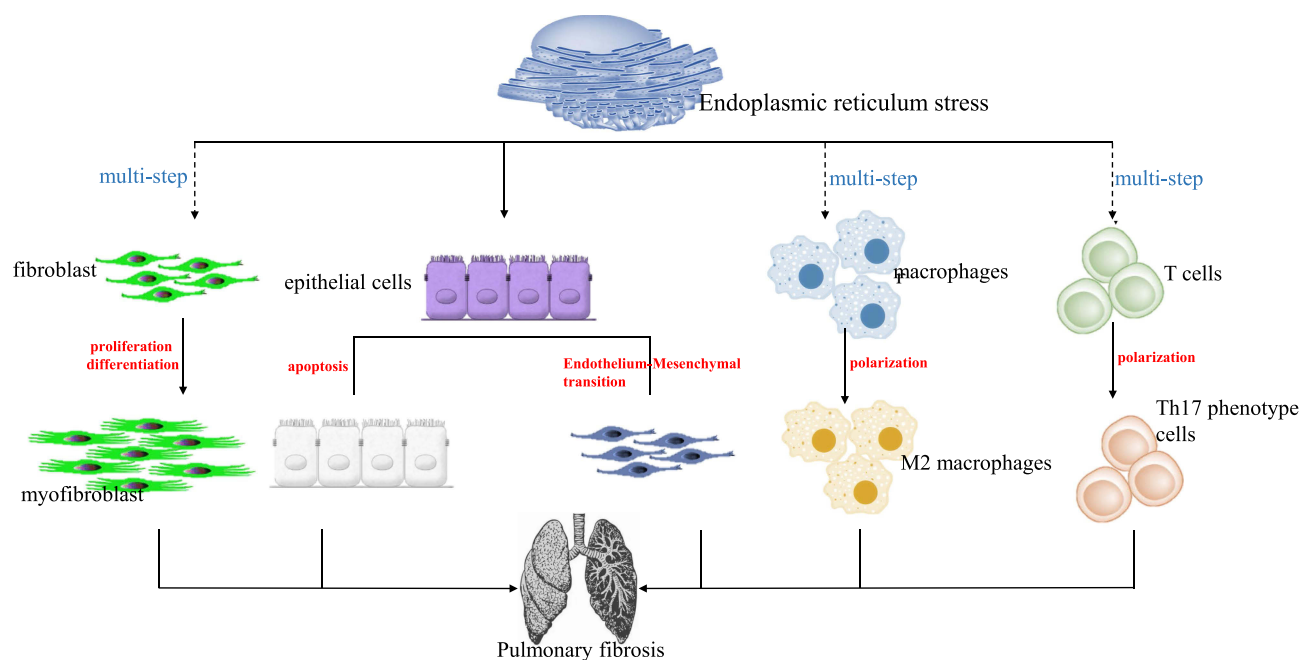


Figure 2 The effect of ERS in different cell types on pulmonary fibrosis.

Epithelial Cells

Recent research has proposed that ERS contributes to the progression of IPF. In animal experiment, BLM has been shown to enhance the induction of ERS in AECs, leading to lung injury and fibrosis.⁷⁸ A full range of ERS markers including ATF4, ATF6, CHOP, and BIP have been found to have overexpression in AECs in the lung tissues of IPF patients.^{79,80} Surfactant Protein C (SP-C), a secreted transmembrane protein, is thoroughly found in AEC II. Overexpression of mutant SP-C protein or L188Q SP-C (a mutant form of SP-C) protein will activate the UPR and ER-associated degradation pathways, ultimately resulting in increased AECs apoptosis and lung pathological changes.^{81,82} Bridges et al also confirmed that the increase of exon 4 deleted SP-C protein could enhance sequential ER accumulation, followed by apoptotic cell death.⁸³

Previous studies by Lawson et al have demonstrated that promoted-expression of L188Q SP-C or tunicamycin treatment can induce fibrotic remodeling and AECs apoptosis, suggesting there is a balance between AEC II and UPR. However, the BLM-treated L188Q SP-C mice possessed higher apoptosis of AECs and more numbers of fibroblasts than BLM-treated WT mice. Simultaneously, higher caspase-12 levels have also been observed in lung tissues in BLM-challenged-L188Q SP-C mice.⁷⁸ A recent study also confirmed that L188Q SP-C expression impaired AEC II expansion during postnatal alveolarization, giving rise to a significant and perpetual decrease of AEC II numbers in adult mice, besides that, the level of the mutant allele was related to delayed onset of AEC II proliferation.⁸⁴ Recently, Rodriguez et al have proposed that murine fibrosis models based on SP-C mutations cause activation of the AEC II UPR and ERS.⁸⁵ Collectively, these reports indicate that the relationship between ERS and AECs apoptosis or survival is unclear. It seems that only when the epithelial cells are damaged, the ERS will be more sensitive to fibrotic remodeling.

As is known to us, CHOP, an ERS-induced transcription factor, contributes to the progress of BLM-induced fibrosis in mice lung.⁸⁶ Several other researches have demonstrated that AEC II can induce apoptosis and consecutive fibrosis through promoting the induction of CHOP.^{87,88} Tanaka et al revealed that BLM-induced lung inflammation, apoptosis and fibrosis were attenuated in CHOP gene deficient mice.⁸⁹ Further, Yang et al identified that inhibition of CHOP gene mitigated lung fibrosis through inhibiting Shh/HH signaling pathway in fibroblasts.⁹⁰ Then, Yang et al also indicated that CHOP knockdown promotes engraftment and suppresses the myofibroblast change of lung resident mesenchymal/stromal cells during BLM-induced pulmonary fibrosis.⁹¹ These findings indicate that targeting CHOP may be a promising way to treat pulmonary fibrosis.

Fibroblasts

Although the repeated epithelial micro-injury is defined as a driver for IPF pathology, more and more studies have pointed that how fibroblasts respond to both nearby cells and the damaged microenvironment is a critical issue to be addressed. And, the proliferation, migration and differentiation of fibroblasts have been found to facilitate the occurrence and progression of lung fibrosis.^{20,92–95}

ERS and the UPR are known to facilitate the development of lung fibrosis by regulating myofibroblast proliferation and differentiation.^{42,88,96,97} Lately, accumulating researches have pointed out the importance of ERS with regard to fibroblast during lung fibrosis.⁹⁸ Baek et al provided the first evidence that the activation of UPR could promote differentiation of fibroblasts during fibrosis.⁹⁹ TGF- β 1-induced obviously increased expression of BIP, XBP-1, and ATF6 α protein, which were coincided with an up-regulation of α -SMA and collagen I in mice or human fibroblasts. Further, 4-Phenylbutyric acid (4-PBA), as a chemical chaperone, evidently inhibited TGF- β 1-induced myofibroblasts differentiation with increasing the activation of UPR, α -SMA and collagen.^{99,100} Cao et al have indicated that SiO₂ exposure promotes the accretion of misfolded protein with triggering UPR in fibroblast, which conduces to the upregulation of ERS-related proteins.¹⁰¹ A similar result reported by Cheng et al found that ERS was activated in L929 and HPF-a cells induced by SiO₂, which promoted activation of fibroblasts.¹⁰² In addition, PI3K/AKT signaling, upstream of ERS, can regulate fibroblast proliferation and differentiation, resulting in BLM-induced lung fibrosis.⁴² In fact, ERS can also activate fibroblast proliferation. ERS was activated in the course of myofibroblasts differentiation of human lung fibroblasts treated with cigarette smoke.¹⁰³ Thioredoxin domain-containing protein 5 (TXNDC5), a resident ER protein, has been observed to participate in fibroblasts activation.¹⁰⁴ A study has revealed that TXNDC5 is associated with excessive fibroblast activation, proliferation, and ECM production.¹ Chen et al also revealed that IRE1 α -XBP-1 signaling pathway was bound up with TXNDC5 in crystalline silica-induced pulmonary fibrogenesis model.¹⁰⁴ Lee et al also confirmed that TXNDC5 promoted fibrogenesis by strengthening TGF- β 1 signal via direct binding with TGFBR1 in fibroblasts.¹ Overall, available data indicate that ERS conduces to a vulnerable fibroblast activation state in lung fibrosis. However, further research on pathological mechanism in lung fibrosis is still needed.

M2 Macrophages

In addition to endothelial injury and myofibroblasts differentiation, ERS can alter the phenotype of immune/inflammatory cells, particularly macrophages. The enhanced M2 macrophages polarization can prompt fibroblast activation through secreting profibrotic mediators (such as TGF- β 1, platelet-derived growth factor (PDGF), matrix metalloproteinase 9 (MMP-9), tissue inhibitors of metal proteinase 1 (TIMP1), and CCL18).^{105–108} Accumulating evidence has revealed that ERS is pivotal in macrophage phenotypes, particularly in M2 macrophage polarization.^{109–111} Ryan et al have demonstrated that the expression of ERS genes in alveolar macrophages from patients with IPF or from mice with a fibrotic phenotype are up-regulated.¹¹² In alveolar macrophages obtained from mice with fibrosis or allergic airway inflammation, the elevated CHOP expression along with ERS can modulate the generation of M2 macrophages, which then trigger development of lung fibrosis. Similarly, the deficiency of CHOP can attenuate the generation of M2 macrophages.¹¹⁰ Oh et al have demonstrated that the promoted ERS is necessary to the generation of the M2 macrophages through regulating JNK and PPAR γ . Similarly, suppression of ERS shifted differentiated M2 macrophages toward an M1 phenotype.¹¹¹ These literatures reveal that ERS (particularly CHOP) is associated with the M2 macrophage polarization, contributing to progression of fibrosis. However, the precise mechanism of how ERS signaling pathway participates in M2 macrophages still remains elusive.

Nonetheless, the role of ERS in macrophage is protective in several models of lung fibrosis. Apoptosis of macrophage plays an important role in host protection against mycobacterial infections.¹¹³ In the present study, ERS mediated macrophages apoptosis is thought to be crucial in host defenses against intracellular pathogens.¹¹⁴ Then, a recent study showed that the weakened PERK-eIF2 α -ATF4 signal pathway could reduce THP-1 macrophages apoptosis and promote mycobacteria survival in the infected-macrophages.¹¹⁵ ERS markers (BIP and CHOP)-mediated macrophage apoptosis can protect against BLM-induced fibrosis.¹¹⁶ Hu et al have reported that silica-stimulated ERS is involved in the apoptosis of alveolar macrophages.¹¹⁷ The calcium-induced potassium ion channel KCa3.1 has been explicitly implied as a prospective treatment method to fibrotic diseases, especially IPF.^{118–120} Importantly, activation of the KCa3.1 ion channel induces cells including fibroblasts, macrophages, and epithelial cells in IPF.¹¹⁸ Perera et al discovered that barricade of the KCa3.1 ion channel mitigates the ERS and apoptosis in AEC II and macrophages.¹²¹ These data disclose

that ERS in macrophage may act as protective or harmfulness effects, whereas ERS-induced apoptosis of M2 macrophages could be a great force and new treatment strategy to alleviate fibrosis in lung.

Th17 Cell Differentiation

In addition to innate immunity, ERS/UPR signaling is involved in the adaptive immune system. Differentiation of Th17 cells calls for two cytokines, including IL-6 and TGF- β .¹²² Th17 cells differentiation has been verified to be in connection with lung fibrosis.^{123,124} Preliminary studies have revealed that the CD147 protein is increased during pulmonary fibrosis.¹²⁵ Geng et al have shown that CD147 promotes M1 macrophage and stimulates the differentiation of Th17 cells in lung interstitial fibrosis, perhaps through regulating IL-6, IL-1 β , IL-12, and IL-23.¹²⁶ In particulate matter (PM_{2.5})-induced lung fibrosis model, the activation of IL-17 and Th17 cell differentiation was observed.¹²⁴ Dong et al have demonstrated that IL-27 mitigates BLM-induced fibrosis through modulating Th17 differentiation and cytokine secretion in lung.¹²⁷ It has been proposed that inhibition of Th17 cell differentiation can result in attenuation of pulmonary fibrosis.¹²⁸ Brucklacher et al have demonstrated that ERS-induced by hypoxia or nutrient deprivation can facilitate Th17 cell differentiation via sustained cytoplasmic calcium levels.¹²⁹ These results revealed that Th17 cells differentiation may be a significant factor for the development of IPF.

Potential Therapeutic Approach

Mechanisms of Potential Target-TXNDC5 or STING

TXNDC5, an ER-localized protein disulfide isomerase, can catalyze the rearrangement of disulfide bonds. TXNDC5 acts as a molecular chaperone to reduce abnormal protein synthesis, promote ECM protein folding, and contribute to ECM protein stability.¹³⁰ Numerous studies have shown that TXNDC5 is significantly up-regulated in lung and lung fibroblasts of IPF patients or mice by BLM-induced fibrosis. TXNDC5 promotes fibrogenesis by directly binding to TGF- β 1 receptors and stabilizing TGF- β 1 signaling in lung fibroblasts. In addition, in lung fibroblasts, TXNDC5 is upregulated by TGF- β 1 stimulation s through ERS/ATF6-dependent transcriptional control.¹ Chen et al also pointed the importance of IRE1 α -TXNDC5 signaling to fibroblast activation.¹⁰⁴ In addition to pulmonary fibrosis, TXNDC5 also plays a promoting role in other fibrotic diseases. The research group of Chen et al has demonstrated that TXNDC5 is an important promoting factor of cardiac fibrosis through promoting ECM deposition and fibrosis activation by redox-sensitive c-Jun N-terminal kinase signaling. TXNDC5 deletion protects against β agonist-induced fibrosis.¹³⁰ Besides, Chen et al demonstrated that loss of TXNDC5 in kidney fibroblasts extenuated the progression of established fibrosis, hinting the potential of TXNDC5 for intervening renal fibrosis and chronic kidney diseases¹³¹ (Figure 3).

Stimulator of interferon genes (STING), namely Transmembrane protein 173 (TMEM173), is an ER-associated membrane protein activated by cyclic GMP-AMP synthase (cGAS), DEAD-box helicase 41 (DDX41) and interferon-inducible protein 16 (IFI16), in reaction to binding either host- or pathogen-derived cytosolic double-stranded DNA (dsDNA) or cyclic dinucleotides (CDNs).^{132,133} Increasing studies revealed the relevance and cross-regulation between the ER and STING, where the ERS known as the UPR brings into focus.¹³⁴ Deng et al indicated that STING-mediated ERS signal pathway was activated in lung fibrosis mice.⁴⁰ Zhang et al showed that deletion of STING can mitigate the expression of ERS-related proteins PERK, eIF2 α and IRE1 α .¹³⁵ In turn, ERS perhaps induce activation of STING in one way or another lacking the mitochondrial intermediary, for example through stabilizing STING oligomerization or shifting STING trafficking, while the definitive mechanism has been unclear. Since unbalanced cell death processes are involved in lung fibrosis, current evidence indicates that the deletion of STING causes an aggravated fibrosis independently of type I IFN signaling and featured with a prolonged inflammation¹³⁶ (Figure 4). In addition to pulmonary fibrosis, STING also plays a promoting role in other fibrotic diseases. Xiao et al described that STING-IRF3-NLRP3 signaling promotes hepatocyte pyroptosis and hepatic inflammation in liver fibrosis.¹³⁷ H-151, a selective inhibitor of the cGAS-STING signaling pathway, can mitigate cardiac fibrosis by preserving myocardial function after myocardial infarction.¹³⁸ The STING-PERK-eIF2 α signaling pathway makes a significant contribution to cellular senescence and organ fibrosis. Targeting the cGAS-STING-PERK signaling pathway mitigated lung and kidney fibrosis.¹³⁹

These data indicated that targeting TXNDC5 or STING may be a forceful therapeutic strategy to alleviate lung fibrosis, and then improving pulmonary function and medical prognosis in patients with IPF.

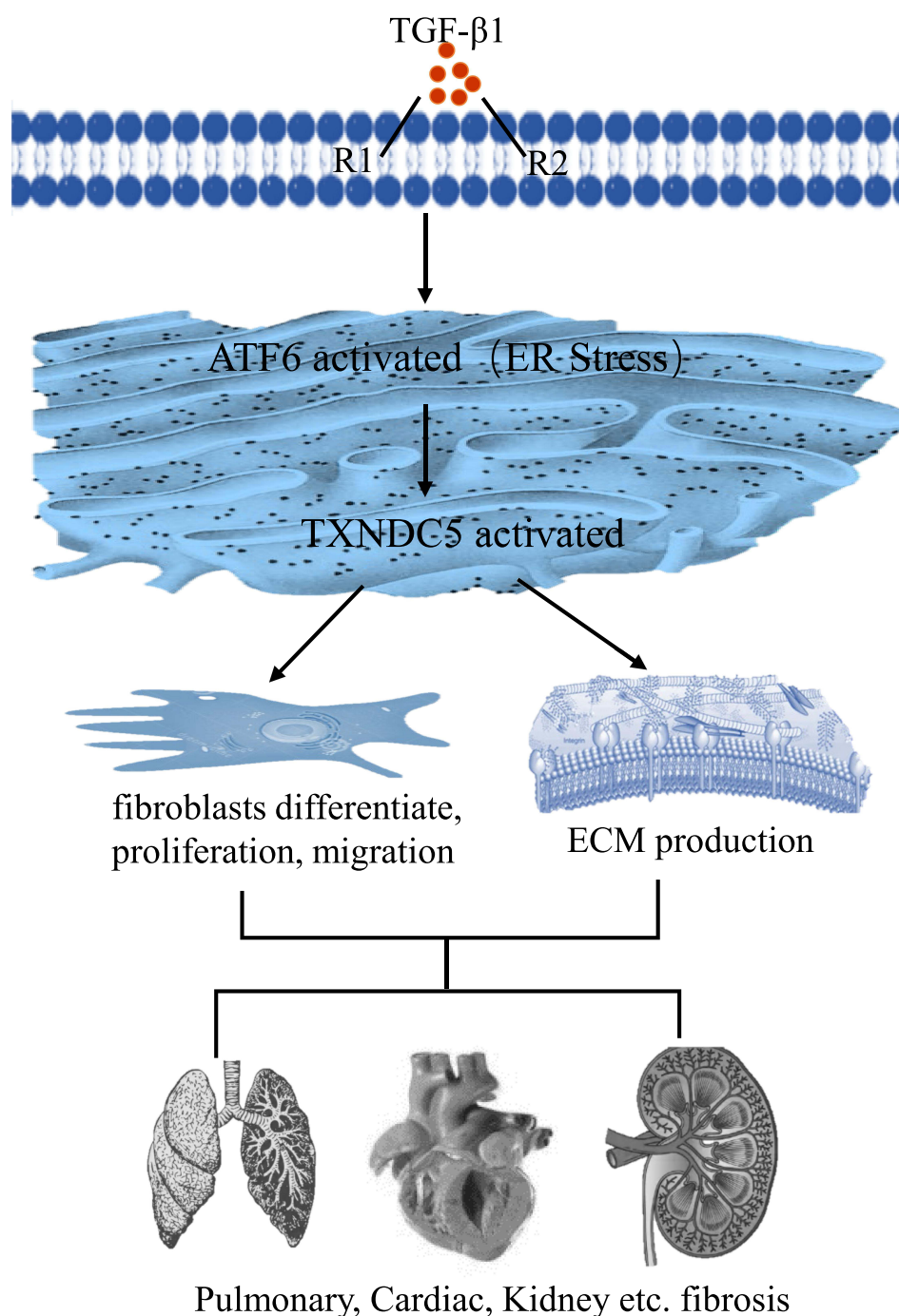


Figure 3 Mechanisms of potential target-TXNDC5.

Natural Products Alleviate Pulmonary Fibrosis via Regulating Endoplasmic Reticulum Stress

Currently, only the two drugs, pirfenidone and nintedanib, are able to postpone IPF progression, but drugs neither improve or even stabilize lung function and enhance quality of life. More importantly, the two therapeutic drugs have undesirable adverse effects, including gastrointestinal tract (nausea, diarrhea and dyspepsia, et al), skin reactions (rash and photosensitivity, et al), nervous system, diarrhea, and nausea.^{140–142} Consequently, it is in a popular to develop new drugs for IPF with fewer poisonousness and side reactions. Nowadays, over decades of researches into the mechanism of

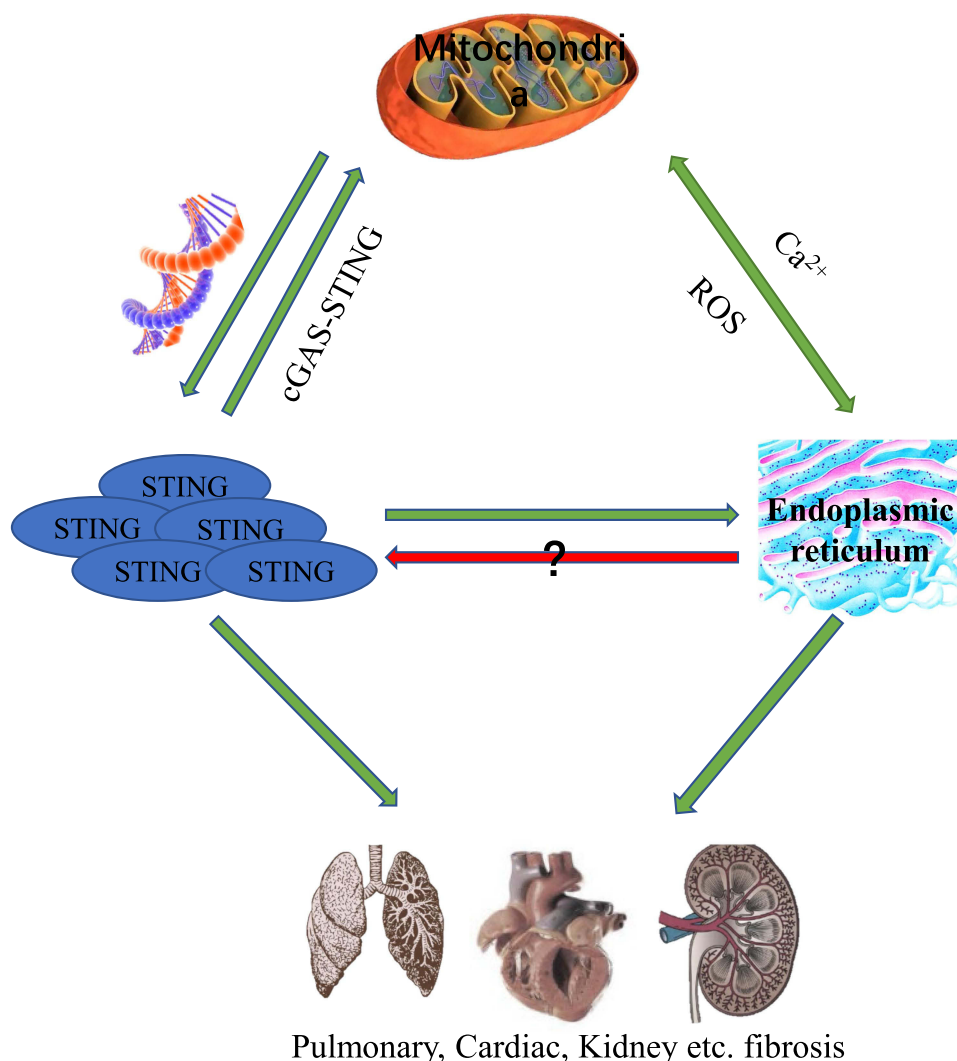


Figure 4 Mechanisms of potential target-STING.

IPF, ERS has been defined to be crucial. A variety of ERS-related proteins are associated with fibrotic response, and under certain condition, inhibition of these important factors were in connection with improvement of lung fibrosis.⁵⁰ Then, the natural products which have proven to provide benefits in IPF treatment by regulating ERS are summarized and categorized (Tables 1 and 2) (Figures 5 and 6).

Bioactive Compounds

Naringin

Naringin is a naturally resourced flavanone glycoside mainly existed in grapefruit and citrus fruits.¹⁶⁶ Previous studies have identified that naringin possesses diverse pharmacological activities such as anti-inflammatory and anti-oxidative stress.^{167,168} It has been reported that naringin shows potential benefits to withstand BLM-induced fibrosis in vivo with reducing the level of inflammatory cytokines (TNF- α , IL-6, and IL-1 β), regulating oxidative stress markers (MDA, SOD, and GSH-Px) and regulating the apoptosis-related genes (Bax and Bcl-2). Moreover, it has been revealed that naringin can inhibit ERS and mitophagy-related genes (BIP, PERK, p-eIF2 α , ATF4, LC-3B, p62, and Parkin), thereby activating ATF-3 and suppressing PINK1. Thus, naringin may be an up-and-coming therapeutic active ingredient for treating IPF through inhibiting ERS, decreasing apoptosis, and keeping mitochondrial homeostasis, which may be related to its modulation of ATF3/PINK1 pathway.¹⁴³

Table I Bioactive Compound Ameliorate Pulmonary Fibrosis by Regulating Endoplasmic Reticulum Stress

Name	Types	In vitro/in vivo Model (Effective Dose) Cell (Effective Concentration)	Related Pharmacological indicators	Related Molecular Mechanisms	Refs.
Naringin 1	Flavonoids	BLM (100mg/kg)	HYP↓ TNF- α ↓ IL-6↓ IL-1 β ↓ HYP↓ TGF- β 1↓ α -SMA↓ collagen III↓ MDA↓ SOD↑ GSH-Px↑ BIP↓ PERK↓ p-eIF2 α ↓ ATF4↓ Bax↓ Bcl-2↑ LC-3B↑ p62↓ PINK1↑ Parkin↑	Inhibition of ATF3/PINK1 and ERS signaling axis Inhibition of inflammation and oxidative stress Inhibition of apoptosis Activation of mitophagy	[143]
Pachymic acid 2	Terpenes	BLM (40 mg/kg)	α -SMA↓ HYP↓ TGF- β 1↓ collagen I↓ Fibronectin↓ MDA↓ ROS↓ ATP↑ SOD↑ CAT↑ BIP↓ CHOP↓ Caspase 9↓ ATF4↓	Inhibition of oxidative stress Inhibition of apoptosis Inhibition of BIP/ATF4 signaling pathways	[144]
Triptolide 3	Terpenes	BLM (1.0 mg/kg)	BIP↓ CHOP↓	Inhibition of apoptosis Inhibition of BIP signaling pathways	[145]
Tauroursodeoxycholic acid 4	Steroids	BLM (250 mg/kg) Hypoxia (100 mg/kg) A549 (0.5 mmol/L)	α -SMA↓ E-cadherin↑ TGF- β 1↓ HYP↓ IL-1 β ↓ p-Smad2↓ p-Smad3↓ Ki67↓ PCNA↓ HO-1↓ 3-NT↓ BIP↓ CHOP↓ p-PERK↓ p-eIF2 α ↓ ATF4↓ ATF6↓ XBP-1s↓ p58 ^{IPK} ↓ caspase-12↓ caspase-3↓ TSP-1↓ Caspase-1↓ GRP94↓ HRD1↓ SEL1L↓ parkin↓	Inhibition of oxidative stress Inhibition of TGF- β /Smad2/3-mediated EMT Inhibition of BIP/PERK eIF2 α /ATF6 signaling pathways Inhibition of apoptosis Inhibition of TSP-1/TGF- β 1 signaling pathway	[89,146–148]
Engeletin 5	Flavonoids	BLM (25 mg/kg) L929 (270 μ g/mL)	α -SMA↓ collagen I↓ E-cadherin↑ Vimentin↓ Snail↓ BIP↓ ATF4↓ PERK↓ CHOP↓ p-Smad2/3↓ p-JNK↓	Inhibition of BIP/PERK/ATF4 signaling pathways Inhibition of TGF- β 1-smad2/3 and JNK signaling pathways	[149]
Spermidine 6	Polyamines	BLM (50 mg/kg) mouse primary ATII (100 μ mol/L)	P16↓ p21↓ HYP↓ TNF- α ↓ TGF- β 1↓ IL-1 β ↓ CHOP↓ BIP↓ ATF6↓ IRE-1↓ caspase-3↓ LC3B II/ I↑ ATG7↑ beclin-1↑ p-mTOR↓	Inhibition of inflammation Inhibition of apoptosis Activation of autophagy Inhibition of BIP/ATF6 signaling pathway	[150]
Salidroside 7	Terpenes	BLM (150 μ g/kg) primary fibroblasts (5 μ mol/L)	BIP↓ CHOP↓ ATF-4↓ XBP-1↓ p-AKT↓ p-mTOR↓ p-p70S6K↓	Inhibition of PI3K/AKT signaling pathway Inhibition of BIP/ATF4 signaling pathway	[151]
Ginsenoside Rb1 8	Terpenes	Paraquat (120 mg/kg)	TNF- α ↓ IL-6↓ IL-1 β ↓ BIP↓ β -catenin↓ MMP2↓	Inhibition of inflammation Inhibition of BIP signaling pathway	[152]
Curcumin 9	Phenols	BLM (30 mg/kg) WI-38 (5 μ mol/L)	α -SMA↓ CCN2↓ collagen I↓ vimentin↓ p-JNK↓ p-p38↓ p-ERK↓ PERK↓ miR-19a↑ miR-19b↑ miR-26b↑	Inhibition of JNK and PERK signal pathway	[153]
Isorhamnetin 10	Flavonoids	BLM (30 mg/kg) A549 (100 μ mol/L) HBEC (100 μ mol/L)	α -SMA↓ collagen I↓ E-cadherin↑ BIP↓ CHOP↓ vimentin↓ TGF- β 1↓ p-PERK↓ p-eIF2 α ↓	Inhibition of EMT Inhibition of ERS and PERK signaling pathway	[154]
Chlorogenic acid 11	Phenols	BLM (60 mg/kg) RLE-6TN (50 μ g/mL)	α -SMA↓ Collagen I↓ CHOP↓ BIP↓ p-PERK↓ p-IRE-1↓ cleaved-ATF-6↓ cleaved-Caspase-12↓ cleaved-Caspase-9↓ cleaved-Caspase-3↓	Inhibition of apoptosis Inhibition of ERS and PERK signaling pathway	[155]
Melatonin 12	Alkaloids	BLM (5 mg/kg)	HYP↓ α -SMA↓ ATF-6↓ BIP↓ p-eIF2 α ↓ p-IRE1 α ↓ XBP-1↓ p-JNK↓	Inhibition of ATF6/eIF2 α /IRE1 signaling pathway	[77]

Note: The number represents the corresponding bioactive compound.

Table 2 Herbal Preparation Ameliorate Pulmonary Fibrosis by Regulating Endoplasmic Reticulum Stress

Herbal Preparation	Major Plants	In vitro/in vivo Model (Effective Dose) Cell (Effective Concentration)	Related Pharmacological Indicators	Related Molecular Mechanisms	Refs.
Tanreqing injection I	<i>Scutellaria baicalensis</i> Georgi (Huangqin, 23.6%) <i>Selenaretos thibetanus</i> Cuvier (Xiongdanfen, 3.8%) <i>Capra hircus</i> Linnaeus (Shanyangjiao, 1.9%) <i>Lonicera japonica</i> Thunb. (Jinyinhua, 23.6%) <i>Forsythia suspensa</i> (Thunb.) Vahl (Lianqiao, 47.1%)	BLM (5.2 mL/kg)	TNF- α ↓ IL-6↓ IL-1 β ↓ HYP↓ TGF- β 1↓ α -SMA↓ collagen I↓ E-cadherin↑ STING↓ p-P65↓ p-PERK↓ p-eIF2 α ↓ BIP↓ ATF4↓	Inhibition of STING-mediated PERK/eIF2 α /ATF4 signaling pathway Inhibition of inflammation	[40]
Bushen Yifei Xiaozheng Decoction 2	<i>Rehmannia glutinosa</i> (Gaert.) Libosch. ex Fisch. et Mey. (Shudihuang) <i>Angelica sinensis</i> (Oliv.) Diels (Danggui) <i>Citrus reticulata</i> Blanco (Chenpi) <i>Pinellia ternata</i> (Thunb.) Ten. ex Breitenb. (Banxia) <i>Fritillaria thunbergii</i> Miq. (Zhebeimu) <i>Whitmania pigra</i> Whitman (Shuizhi) <i>Glycyrrhiza uralensis</i> Fisch. (Zhigancao)	BLM (12.68 g/(kg·d)) A549 (200 μ g/mL)	SP-C↓ α -SMA↓ E-cadherin↑ BIP↓ IRE1↓ TRAF2↓ p-JNK↓ PERK↓ CHOP↓ Bax↓	Inhibition of JNK signaling pathway Inhibition of BIP/PERK/IRE1 signaling pathway Inhibition of apoptosis	[156–159]
Citrus alkaline extract 3	<i>Citrus reticulata</i> Blanco	BLM (96 mg/kg) A549 (200 μ g/mL) MRC-5 (200 μ g/mL)	Collagen I↓ collagen III↓ PERK↓ p-eIF2 α ↓ BIP↓ ATF4↓ ATF3↓ PINK1↑	Inhibition of ATF3/PINK1 signaling pathway	[160]
Maimendong Decoction 4	<i>Radix Ophiopogonis</i> (Maimendong) <i>Rhizoma Pinelliae</i> (Banxia) <i>Radix et rhizoma ginseng</i> (Renshen) <i>Radix glycyrrhizae</i> (Gancao) <i>Fructus Jujubae</i> (Dazao) <i>Oryza sativa</i> L. (Jingmi)	BLM (2.4 g/100 g)	HYP↓ α -SMA↓ SPC↑ BIP↓ CHOP↓	Inhibition of apoptosis Inhibition of BIP signal pathway	[161]
Gualou Xiebai Decoction 5	<i>Trichosanthes kirilowii</i> Maxim. (Gualou) <i>Allium macrostemon</i> Bunge (Xiebai)	BLM (2.8 g/kg)	p-PERK↓ p-IRE1 α ↓ BIP↓ ATF6 α ↓	Inhibition of BIP/PERK signal pathway	[162]

(Continued)

Table 2 (Continued).

Herbal Preparation	Major Plants	In vitro/in vivo Model (Effective Dose) Cell (Effective Concentration)	Related Pharmacological Indicators	Related Molecular Mechanisms	Refs.
Yougui drink 6	<i>Rehmannia glutinosa</i> (Gaert.) Libosch. ex Fisch. et Mey. (Shudihaung) <i>Dioscorea polystachya</i> Turczaninow (Shanyao) <i>Cornus officinalis</i> Sieb. et Zucc. (Shanzhuyu) <i>Glycyrrhiza uralensis</i> Fisch. (Zhigancao) <i>Cinnamomum cassia</i> (L.) D. Don (Rougui) <i>Eucommia ulmoides</i> Oliv. (Duzhong) <i>Lycium chinense</i> Miller (Gouqizi) <i>Aconitum carmichaelii</i> Debeaux (Fuzi)	BLM (1 g/mL)	HYP↓ PGE ₂ ↓ BIP↓ CHOP↓ caspase-3↓	Inhibition of apoptosis Inhibition of BIP signal pathway	[163]
Dan Shao Hua Xian Capsule 7	<i>Salvia miltiorrhiza</i> Bunge (Danshen) <i>Paeonia lactiflora</i> Pall (Chishao) <i>Astragalus membranaceus</i> (Fisch.) Bge. var. <i>mongholicus</i> (Bge.) Hsiao (Huangqi) <i>Ginkgo biloba</i> L. (Yinxingye) et al	BLM (0.8 g/(kg d))	BIP↓ NF-κB↓ HYP↓ MDA↓ SOD↑	Inhibition of oxidative stress Inhibition of BIP signal pathway	[164,165]

Note: The number represents the corresponding herbal preparation.

Pachymic Acid

Pachymic acid is a bioactive ingredient of *Poria cocos* with various pharmacological properties, including anti-tumor, anti-inflammatory, antioxidant, hypoglycemic, and sedative hypnosis.¹⁶⁹ Furthermore, pachymic acid possesses beneficial effects against fibrosis. Li et al reported that pachymic acid alleviated rat pancreatic injury and fibrosis with pancreatitis, and the inhibition of NLRP3 inflammasome is involved.¹⁷⁰ Furthermore, in rats with BLM-induced pulmonary fibrosis, pachymic acid also showed benefits with decreasing the expressions of HYP and TGF-β1, and regulating oxidative indicators (MDA, SOD, CAT, and ROS).¹⁴⁴ Importantly, pachymic acid treatment also could down-regulate the levels of ERS-related proteins (BIP, CHOP, caspase-9, and ATF4). Collectively, pachymic acid may alleviate BLM-induced lung fibrosis and pathological injury in vivo by inhibiting ERS and improving mitochondrial function.¹⁷⁰

Triptolide

Triptolide, a diterpenoid triepoxide, is the active component of *Tripterygium wilfordii* Hook F. Triptolide has been proved to various prospective pharmacological effects, including anti-cancer, anti-tumor, anti-obesity and anti-diabetes.¹⁷¹ Previously, the study of triptolide on BLM-induced fibrosis in mice lung were conducted. The pulmonary function

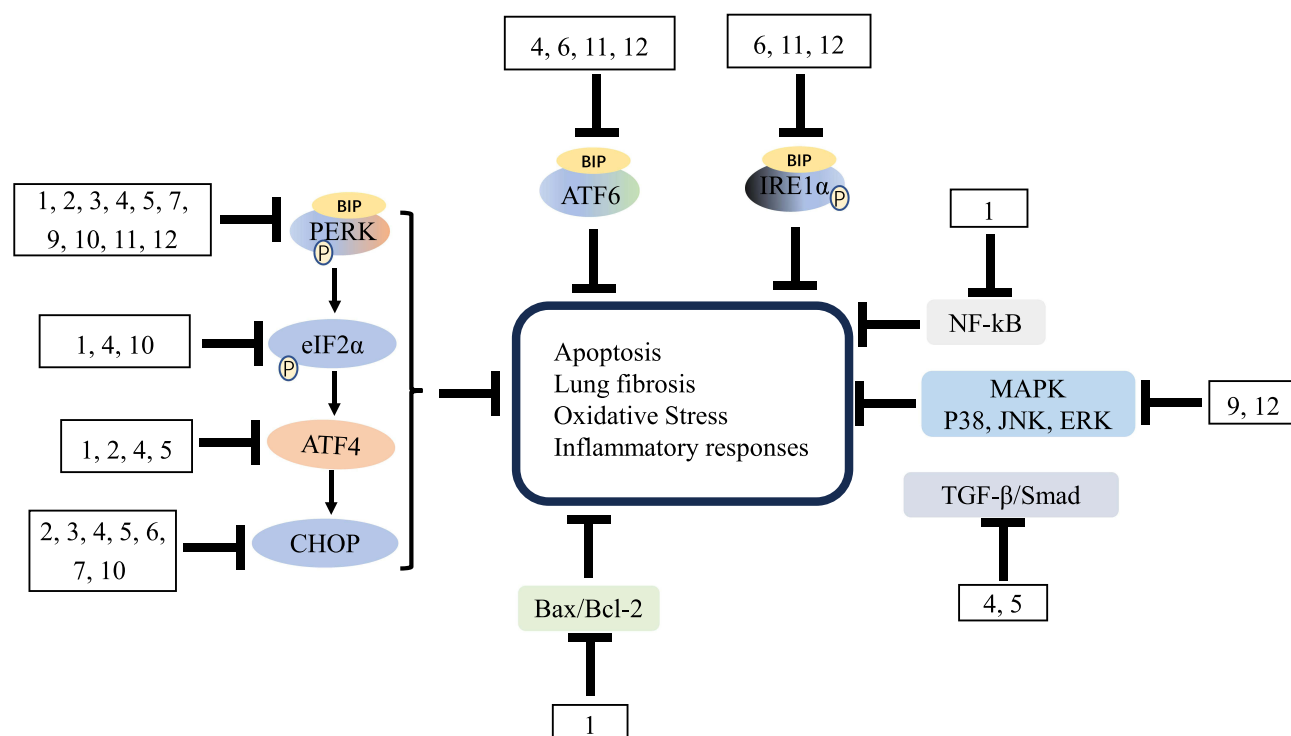


Figure 5 The mechanisms underlying the inhibitory effects of bioactive compounds on lung fibrosis. The number represents the corresponding bioactive compound. The arrow refers to the role of promotion, the "T" refers to the role of inhibition.

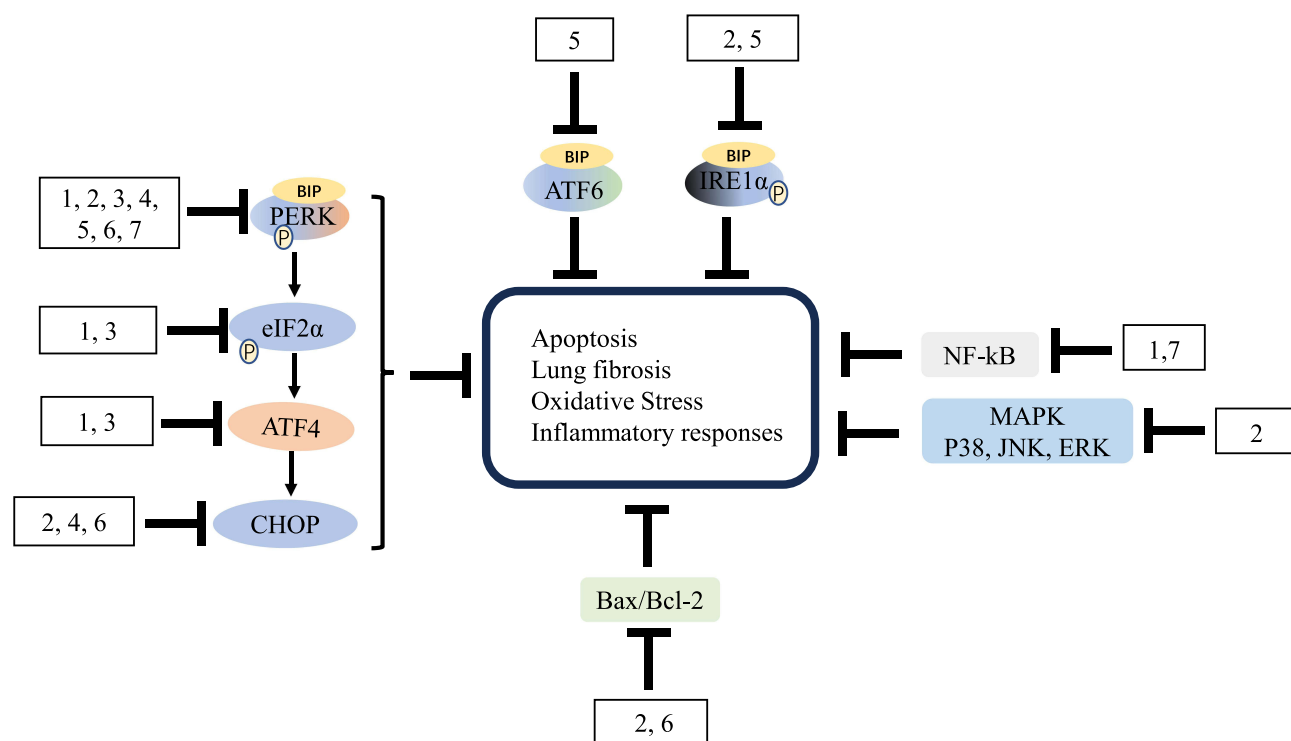


Figure 6 The mechanisms underlying the inhibitory effects of herbal preparation on lung fibrosis. The number represents the corresponding herbal preparation. The arrow refers to the role of promotion, the "T" refers to the role of inhibition.

indicators such as FVC, mass FVC, and Cydn were up-regulated, and FEV0.4/FVC, RI, and RE were down-regulated in the triptolide treated groups. Moreover, triptolide can mitigate the seriousness of alveolitis and fibrosis by downregulating the abnormal expression of BIP and CHOP, indicating the inhibition ERS is involved in the triptolide against lung fibrosis.¹⁴⁵

Tauroursodeoxycholic Acid

Tauroursodeoxycholic acid (TUDCA), a molecular chaperone, has been proved to decrease ERS via promoting protein folding and transporting.¹⁷² According to the recent research, it has been demonstrated that TUDCA mitigated non-liver diseases, for instance intestinal inflammation and neurodegenerative disorders through reducing ERS.^{173,174} Additionally, TUDCA has displayed a therapeutic effectiveness of lung fibrosis. Firstly, TUDCA treatment repressed ERS-related molecules/events (ATF6 and eIF2a) and subsequently alleviated paraquat-caused pulmonary fibrosis.¹⁴⁶ Another study also demonstrated that in BLM-caused lung fibrosis, TUDCA not only prevented the BLM-induced fibrotic changes (the HYP content and histological scores), but also suppressed inflammations (total protein and leucocytes, peculiarly neutrophils), and IL-1 β , caspase-11, IRE1, eIF2a, XBP-1, and CHOP.⁸⁹ Then, addition to BLM-induced lung fibrosis model, TUDCA also inhibited PERK pathway-dependent ERS activation in chronic intermittent hypoxia (IH)-induced model. The levels of TGF- β 1 and TSP-1 mRNAs were up-regulated after IH induction; however, these changes were reduced by administration of TUDCA. Moreover, TSP-1/TGF- β 1 pathway is in relation to the protection of TUDCA against IH-stimulated lung fibrosis.¹⁴⁷ The latest research showed that TUDCA reduced excessive cell proliferation and ECM in BLM-stimulated fibrosis model. Moreover, TUDCA prevents pulmonary TGF- β /Smad2/3-mediated EMT and fibrosis in part via inhibiting BLM-induced oxidative stress and ERS (BIP, p-PERK, p-eIF2 α , ATF4, ATF6, and XBP-1s).¹⁴⁸ Thus, TUDCA may have potential preventive and therapeutic effects for inhibiting apoptosis, oxidative stress, and fibrosis.

Engeletin

Engeletin, a flavonoid glycoside, was largely obtained from the dry rhizome of Liliaceae plant *Smilax china* L., shows a variety of potentially beneficial effects, for instance, inhibiting inflammation and oxidative stress.^{175,176} In a study, protective action of engeletin against BLM-induced lung fibrosis and TGF- β 1-induced L929 cells were investigated. The results demonstrated that engeletin suppressed myofibroblast activation and ameliorated lung structure. Engeletin administration remarkably decreased the expression of collagens I and III, α -SMA, and vimentin in vivo and in vitro. RNA sequencing unveiled that PERK/ATF4 signaling pathway in relation to ERS was involved in antifibrotic actions of engeletin. Furthermore, engeletin treatment decreased the expressions of ATF4, CHOP and BIP, which was dependent on its inhibition of p-smad2/3, p-JNK, and lnc949. Overall, engeletin may be a new and promising therapeutic drug for lung fibrogenesis through suppressing ERS via lnc949-mediated TGF- β 1-Smad2/3 and JNK were upstream signaling pathways.¹⁴⁹

Spermidine

Spermidine is prevailing in living organisms as a natural polyamine.¹⁷⁷ Spermidine exerts various activities, including antioxidant, anticancer, anti-oxidative, and anti-inflammatory.¹⁷⁸ The actions of spermidine in BLM-induced lung fibrosis mice were also studied. BLM stimulated the upregulation of β -gal, IL-1 β , TNF- α , and TGF- β 1 in mice and alveolar epithelial cells, while all the changes were inhibited by spermidine therapy. BALF outcomes unveiled that spermidine obviously mitigated inflammatory reaction, including the reduction of macrophages, neutrophils, and lymphocytes. BLM-induced upregulation of ER-related proteins, for instance CHOP, GRP78, ATF6, and IRE-1 were also decreased with spermidine treatment. Thus, exogenous spermidine mitigated lung fibrosis via the downregulation of the ERS signaling pathway. Interestingly, spermidine was able to increase the LC3 I/II ratio and the autophagy-related protein (ATG7 and beclin-1), indicating autophagy may be also involved in the beneficial effects of spermidine in lung fibrosis.¹⁵⁰

Salidroside

Salidroside, a phenylpropanoid glycoside, is the major effective ingredient discovered in all species of *Rhodiola*. A study has revealed that salidroside has the effect of reducing oxidative and inflammatory.¹⁷⁹ The actions of salidroside on BLM-induced lung fibrosis in mouse have been studied, and the results showed that salidroside represented strong anti-fibrotic functions via

suppressing alveolar structure injury and collagen deposition. In addition, salidroside inhibited the levels of ERS associated proteins, including ATF-4, BIP, CHOP, XBP-1, and regulating the levels of PI3K/AKT/mTOR signal proteins, including p-AKT, p-mTOR and p-p70S6K in lung tissues. Thus, perhaps salidroside is a very potential chemical constituent in alleviating BLM-induced pulmonary fibrosis.¹⁵¹

Ginsenoside Rb1

Ginsenoside Rb1 as one of the most prominent compounds in *Panax ginseng* C. A. Mey. has been proved to own various bioactivities, including decreasing oxidative stress and inflammation, balancing cell autophagy, reducing apoptosis, affecting sugar and lipid metabolism, and modulating different cytokines.¹⁸⁰ The protective action of ginsenoside Rb1 on paraquat-induced lung fibrosis has been reported. Paraquat caused a severe respiratory failure and fibrosis in rats, and the inflammatory factors in serum were increased significantly. Otherwise, ginsenoside Rb1 administration inverted the whole biomarkers and cytokine levels, and histopathological changes induced with paraquat. Furthermore, ginsenoside Rb1 inhibited the level of BIP, MMP2 and β -catenin in lung. Thus, the outcome points out a potential part of ginsenoside Rb1 in treating paraquat-induced pulmonary fibrosis.¹⁵²

Curcumin

Curcumin is an active compound extensively extracted from a member of the Zingiberaceae family. Previous researches have exhibited that curcumin holds several pharmacological actions, such as apoptosis, antiatherosclerosis, anti-inflammation, and antithrombotic activities in vitro or in vivo.¹⁸¹ In BLM-treated mice, the levels of α -SMA, CCN2, and vimentin were markedly upregulated, which were reversed by an intraperitoneal injection of curcumin. Furthermore, curcumin suppressed fibroblast differentiation in BLM-treated mice lung tissues, and suppressed endothelin-1 or thrombin-induced MAPK activation and PERK protein level in WI-38 cells. Additionally, curcumin reversed endothelin-1 or thrombin-induced decrease of miR-19a, miR-19b, and miR-26b levels, which contributed to curcumin-mediated suppression of CTGF generation and fibroblast differentiation.¹⁵³

Isorhamnetin

Isorhamnetin is a flavonol aglycone obtained from the plant *Hippophae rhamnoides* L which is extensively used in traditional Chinese medicine (TCM) to the prevention and treatment of various diseases. Isorhamnetin has been proved to be effective components that exert several effects, for instance anti-ERS, antiviral, antitumor, antioxidant, anti-inflammatory, and neurodegenerative injury protection effects.^{182,183} Antifibrosis effect of isorhamnetin on mice lung fibrosis model with BLM was estimated. According to the report, isorhamnetin inhibited BLM-induced collagen deposition, reduced collagen I and α -SMA expression, and alleviated ERS-mediated EMT in vivo. Furthermore, incubation of HBECS and A549 cells with TGF- β 1 markedly activated EMT and ERS, and this effect was reversed by isorhamnetin via PERK pathway. Further investigations are necessary to illuminate the all-round antifibrotic effective of isorhamnetin, and identify the precise mechanism.¹⁵⁴

Chlorogenic Acid

Chlorogenic acid, a naturally occurring non-flavonoid polyphenol, is extensively discovered in green coffee beans, teas, certain fruits, and vegetables. Researches have demonstrated that chlorogenic acid exerts antiviral, antitumor, antibacterial, and antioxidant effects.¹⁸⁴ Importantly, chlorogenic acid (60 mg/kg) significantly suppressed BLM-promoted mesenchymal markers α -SMA and collagen I. Furthermore, chlorogenic acid represented inhibitory actions on the phosphorylation of PERK and ATF-6 in lung tissues. Interestingly, the expressions of cleaved caspase-12, caspase-9 and caspase-3 were evidently upregulated when induced by TGF- β 1, which were significantly suppressed with chlorogenic acid.¹⁵⁵

Melatonin

Melatonin as the main secretory substance of the pineal gland possesses anti-oxidant and anti-inflammatory effect.^{185,186} Moreover, previous research revealed the effective of melatonin in BLM-treated pulmonary fibrosis model.^{187,188} Melatonin clearly mitigated BLM-treated EMT and fibroblasts differentiation, as determined by its inhibition of

a-SMA level. Further information discovered that melatonin markedly mitigated BLM-induced BIP upregulation and elevation of the cleaved ATF6 in the lungs. Additionally, melatonin obviously reduced the level of eIF2 α , a downstream protein of the PERK pathway, as well as IRE1 α phosphorylation. In brief, melatonin alleviates ERS and ERS-mediated EMT in BLM-treated lung fibrosis. Hence, melatonin may be helpful in protecting against IPF.⁷⁷

Herbal Preparation

Tanreqing Injection

As is known to all, Tanreqing injection (TRQ), a Traditional Chinese Patent Medicine, is popular for the syndrome of wind-warm lung fever and phlegm-heat blocking lung. Thus, TRQ is widespread used clinically for various lung diseases, including pneumonia, COPD, and IPF.^{189–193} TRQ comprises five TCMs, namely *Scutellaria baicalensis* Georgi (Huangqin), *Selenaretos thibetanus* Cuvier (Xiongdanfen), *Capra hircus* Linnaeus (Shanyangjiao), *Lonicera japonica* Thunb. (Jinyinhua), and *Forsythia suspensa* (Thunb.) Vahl (Lianqiao).¹⁹⁴ Previous researches have demonstrated that chemical compositions of TRQ are greater than 126 compounds, including flavonoids, phenolic acids, lignans, iridoids, amino acids, phenethyl alcohol glycosides, and steroids, and possesses a series of pharmacological effects, for instance anti-microbial, anti-inflammatory, anti-apoptotic, anti-oxidative, and anti-virus actions.^{190,195,196}

Previously, the promising functions of TRQ in BLM-treated mice lung fibrosis have been estimated. TRQ not only improved lung edema and pulmonary function of mice with lung fibrosis (down-regulated airway resistance and up-regulated lung compliance) but also increased inflammatory responses (down-regulated the number of total cells and neutrophils in BALF, down-regulated inflammatory factors). Additionally, TRQ mitigated collagen synthesis and deposition of lung tissues as well. Moreover, TRQ relieved fibrosis via down-regulating α -SMA and up-regulating E-cadherin. Furthermore, the decreased expression of STING, p-P65, BIP, p-PERK, p-eIF2 α , and ATF4 were also involved in the mechanism of TRQ treatment of IPF. However, further research should pay close attention to the potential mechanisms and the active components for TRQ treatment of IPF.⁴⁰

Bushen Yifei Xiaozheng Decoction

Bushen Yifei Xiaozheng decoction (BSYF), a Chinese herbal prescription, is derived from the classic formula “Jinshui Liu jun decoction”. BSYF comprises six traditional Chinese medicine, including *Rehmannia glutinosa* (Gaert.) Libosch. ex Fisch. et Mey. (Shudihaung), *Angelica sinensis* (Oliv.) Diels (Danggui), *Citrus reticulata* Blanco (Chenpi), *Pinellia ternata* (Thunb.) Ten. ex Breitenb. (Banxia), *Fritillaria thunbergii* Miq. (Zhebeimu), *Whitmania pigra* Whitman (Shuizhi). In clinical, BSYF is used to tonify lung, kidney, phlegm and eliminate disease. IPF belongs to “lump of pulmonary collateral”.^{197,198} Thereby, a series of studies were conducted to estimate the roles of BSYF on BLM-treated lung injury. Yan et al showed for the first time that BSYF could relieve the inflammatory reaction and inhibit deposition of extracellular matrix protein and collagen in diseased region to refrain the process of IPF rats.¹⁹⁹ And then, systemic researches are carried out to clarify the underlying mechanisms. BSYF (12.68 g/(kg·d)) administration significantly decreased the AEC II apoptosis, and interfered the process of EMT in BLM-treated mice, and these effects of BSYF were mediated by the downregulation the abnormal expression of SP-C.^{156,157} Another study identified that BSYF could regulate the expression of CHOP pathway, suppress the ERS (down-regulated PERK) and inhibit the apoptosis (down-regulated Bax) of AEC II, thereby delaying the pathological changes of IPF.¹⁵⁸ Further investigation revealed the underlying mechanism of BSYF inhibiting ERS in IPF. BSYF was given to A549 (200 μ g/mL) after TGF- β 1 administration. On the basis of the results presented, TGF- β 1 dropped markedly the expression of SP-C and α -SMA, and the decrease in E-cadherin. Furthermore, BSYF suppressed TGF- β 1-mediated EMT by inhibiting JNK signaling pathway and the BIP/IRE1 signaling pathway.¹⁵⁹

Citrus Alkaline Extract

Citrus (*Citrus reticulata* Blanco) is used as a food and dietary supplement around the world.²⁰⁰ It is assumed that anti-fibrotic, anti-apoptosis, and anti-senescence effects of *Citrus* is believed to be mediated by its flavonoids and alkaloids.^{201–204} In Wang's study, the effects of Citrus alkaline extract on lung fibrosis induced by BLM in rats were investigated, according to the result of the experiment, Citrus alkaline extract effectively mitigated collagen deposition,

thereby ameliorating fibrosis in vivo. Furthermore, the administration of this extract was found to suppress the BLM or tunicamycin-induced upregulation of ERS biomarker (BIP and PERK), leading to a reduction of ERS levels in lung and A549 cells. What's more, the extract treatment restrained BLM or tunicamycin-treated activation of ERS with increasing ATF-3 and PINK1 expression in vivo or in vitro. These outcomes indicate that *Citrus alkaline* extract acts as a promising therapeutic drug for lung fibrosis. However, further studies were needed to clarify underlying mechanisms of the whole plant extract.¹⁶⁰

Maimendong Decoction

Maimendong Decoction (MMDD) consists of six herbs (*Radix Ophiopogonis* (Maimendong), *Rhizoma Pinelliae* (Banxia), *Radix et rhizoma ginseng* (Renshen), *Radix glycyrrhizae* (Gancao), *Fructus Jujubae* (Dazao), and *Oryza sativa L.* (Jingmi)). In clinical, MMDD is frequently used in China to treat allergic asthma, radiation pneumonitis, chronic bronchitis with lung yin deficiency, pulmonary fibrosis and other respiratory illnesses.^{205–207} It has been confirmed that MMDD contains various chemical constituents, such as Steroidal saponins, 4-O-Demethylophiopogonanone E, methylophiopogonanone A, and liquiritin, and possesses various pharmacological effect of anti-inflammation, anti-oxidative, and anti-apoptosis.^{208–210} Previously, MMDD has been confirmed to alleviate pulmonary fibrosis, improve pulmonary function (FVC), and decrease SP-C expression in BLM-induced fibrotic rats. Importantly, MMDD significantly suppressed the activation of ERS (BIP and CHOP) and cell apoptosis in AEC II. Therefore, the inhibition of ERS and apoptotic pathway in fibrotic lung tissue by MMDD may be involved in the therapeutic effects of MMDD against lung fibrosis.¹⁶¹

Gualou Xiebai Decoction

Gualou Xiebai Decoction (GLXB) is one of the classical prescriptions originally recorded in “Jin Kui Yao Lue” by the famous Chinese physician Zhang Zhongjing in the Han Dynasty. GLXB consists of *Trichosanthes kirilowii* Maxim. (Gualou) and *Allium macrostemon* Bunge (Xiebai) and is clinically used in treating angina pectoris and coronary heart disease.^{211–214} Recent studies have revealed that GLXB exerts anti-oxidative, anti-inflammatory, anti-apoptotic, and anti-fibrotic.^{215–217} Oral administration of GLXB increased the loss in body weight and decreased lung index by BLM-induced. Additionally, GLXB prevented lung histology injury, and relieved the severity of alveolitis and fibrosis by downregulating these abnormal expressions of p-PERK, p-IRE1 α , BIP, and ATF6 α . The findings suggested that GLXB might be a promising drug candidate in treating IPF.¹⁶²

Yougui Drink

Yougui drink (YG) is originally recorded in “Jin Kui Shen Qi Decoction” by the famous Chinese physician Zhang Zhongjing in the Han Dynasty. YG is comprised of *Rehmannia glutinosa* (Gaert.) Libosch. ex Fisch. et Mey. (Shudihaung), *Dioscorea polystachya* Turczaninow (Shanyao), *Cornus officinalis* Sieb. et Zucc. (Shanzhuyu), *Glycyrrhiza uralensis* Sieb. et Zucc. (Shanzhuyu), *Glycyrrhiza uralensis* Fisch. (Zhigancao), *Cinnamomum cassia* (L.) D. Don (Rougui), *Eucommia ulmoides* Oliv. (Duzhong), *Lycium chinense* Miller (Gouqizi), and *Aconitum carmichaelii* Debeaux (Fuzi). It has been defined that YG inhibited oxidative stress, inflammatory, apoptotic and fibrotic.^{163,218,219} In Qiu's experiment, the preventive and therapeutic role of YG on BLM-treated lung injury was discussed. YG administration significantly relieved dysfunction of lung and improved alveolar gas exchange function. Furthermore, YG prevented BLM-induced inflammatory infiltration and collagen deposition in lung tissues through depressing the expression of EP2 in AEC II, elevating the expression of EP3 in macrophage in lung tissues. Additionally, YG delayed lung fibrosis via modulating the levels of BIP and CHOP protein, and improving lung cell apoptosis induced by ERS.¹⁶³

Danshao Huaxian Capsule

Danshao Huaxian Capsule (DSHX), a mixed preparation, is composed of five traditional Chinese herbal medicinal ingredients, including *Salvia miltiorrhiza* Bunge (Danshen), *Paeonia lactiflora* Pall (Chishao), *Astragalus membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao (Huangqi), *Ginkgo biloba* L. (Yinxyngye) et al. DSHX has been used for activating blood, eliminating stasis, clearing heat and removing dampness. The ingredients of DSHX have been

demonstrated to possess therapeutic actions, for instance, anti-inflammatory, anti-fibrosis, anti-oxidation.^{164,220} In Han's study, the role of DSHX on BLM-treated rat pulmonary injuries was discussed. Experimental results have discovered that DSHX markedly diminished the lung HYP contents. Moreover, DSHX ameliorated oxidative stress through down-regulating the MDA level and up-regulating SOD activity. In addition, the alveolitis and fibrosis scores in the pulmonary pathology of the DSHX groups were obviously improved. Further, DSHX postponed the progression of lung fibrosis via down-regulating the level of BIP protein.¹⁶⁴ Simultaneously, another research revealed that DSHX administration significantly relieved lung index and prevented pulmonary fibrosis by suppressing BIP and NF- κ B. Therefore, these findings suggest a potential action of DSHX in treating IPF through inhibiting ERS.¹⁶⁵

Conclusion and Future Directions

There is an ever-increasing scholarly center on the potential therapeutic targets associated with components within the endoplasmic reticulum stress (ERS) response in the treatment of idiopathic pulmonary fibrosis (IPF). Given the crucial role of the unfolded protein response (UPR) in maintaining cellular homeostasis, current research suggests that blocking or extensively inhibiting signaling through one or more branches of the ERS signaling pathway may hold promise as a treatment approach. This review article provides a comprehensive description of the actions on herbal preparations and bioactive compounds by inhibiting ERS in a lung fibrosis model, elucidating the pharmacological actions and underlying mechanisms of these agents. In addition to ERS, the roles of natural compounds have been ascribed to their anti-inflammatory, anti-oxidant, and anti-apoptotic effects, as well as their ability to activate autophagy. Various components may exhibit comparable protective roles and target similar pathways. Notably, in the process of ERS-induced fibrosis, the BIP, PERK, eIF2 α , and ATF4 signaling pathways were frequently implicated. Consequently, phytochemicals hold promise as potential therapeutic agents for IPF. These studies will provide a new direction for natural products to treat IPF via clarifying the pharmacological effects and underlying mechanistic functions of these drugs. Nevertheless, there is an urgent need for further clinical trials to validate the therapeutic efficacy of these compounds against lung fibrosis.

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Disclosure

The authors report no conflicts of interest in this work.

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