



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Traditional Chinese medicine for pulmonary fibrosis therapy: Progress and future prospects



Liu-Cheng Li, Lian-Di Kan*

Department of Pharmacy, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou 310016, China

ARTICLE INFO

Chemical compounds studied in this article:

Baicalein (PubChem CID: 5281605)
 Celastrol (PubChem CID: 122724)
 Curcumin (PubChem CID: 969516)
 Eclipta saponin A (PubChem CID: 476537)
 Paclitaxel (PubChem CID: 36314)
 Paeoniflorin (PubChem CID: 442534)
 Quercetin (PubChem CID: 5280343)
 Tanshinone IIA (PubChem CID: 164676)
 Tectorigenin (PubChem CID: 5281811)
 Triptolide (PubChem CID: 107985)
 α -terpineol (PubChem CID: 17100)

Keywords:

Pulmonary fibrosis
 Traditional Chinese medicine
 Herb
 Active ingredient
 Mechanism

ABSTRACT

Ethnopharmacological relevance: Pulmonary fibrosis (PF) is a chronic, debilitating and often lethal lung disorder. Despite the molecular mechanisms of PF are gradually clear with numerous researchers' efforts, few effective drugs have been developed to reverse human PF or even halt the chronic progression to respiratory failure. Traditional Chinese medicine (TCM), the main component of the medical practice used for more than 5000 years especially in China, often exerts wider action spectrum than previously attempted options in treating human diseases. Recent data have shown the anti-fibrotic benefits of the active ingredients from TCM in this field, which may represent an attractive source of the drug discovery against PF.

Aim of the review: This review summarizes the pre-clinical and clinical evidence on the benefits of TCM and their active ingredients, and provides a comprehensive information and reliable basis for the exploration of new treatment strategies of botanical drugs in the therapy of PF.

Methods: The literature information was obtained from the scientific databases on ethnobotany and ethno medicines (up to Aug 2016), mainly from the Pubmed, Web of Science and CNKI databases, and was to identify the experimental studies on the anti-fibrotic role of the active agents from TCM and the involved mechanisms. The search keywords for such work included: "lung fibrosis" or "pulmonary fibrosis", and "traditional Chinese medicine", "extract" or "herb".

Results: A number of studies have shown that the active agents of single herbs and TCM formulas, particularly the flavonoids, glycosides and alkaloids, exhibit potential benefits against PF, the mechanisms of which appear to involve the regulation of inflammation, oxidant stress, and pro-fibrotic signaling pathways, etc. Besides, the processing methods for discovering TCM in treating PF were prospectively discussed.

Conclusion: These research work have shown the therapeutic benefits of TCM in the treatment of PF. However, more continued researches should be undertaken to clarify the unconfirmed chemical composition and

Abbreviations: ACE, angiotensin converting enzyme; AEC, alveolar epithelial cells; AMs, alveolar macrophages; Andro, Andrographolide; ANG, angiotensin; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; BA, boswellic acids; BAI, Baicalein; BALF, bronchoalveolar lavage fluid; BECs, bronchial epithelial cells; BLM, bleomycin; CAT, catalase; CCl₄, carbon tetrachloride; COL1A1, procollagen type 1 a1; Col-I, collagen types I; COX, cyclooxygenase; CP, cyclophosphamide; CTGF, connective tissue growth factor; DBTG, total glucosides of Danggui-Buxue-Tang; DSQR, Decoction for Strengthening Qi and Replenishing Lung; ECM, extracellular matrix; EGCG, epigallocatechin-3-gallate; EMT, epithelial-mesenchymal transition; EndoMT, endothelial-mesenchymal transition; EOOR, essential oil of Citrus reticulata; ESA, eclipta saponin A; ET, endothelin; FB, fibroblasts; FEV₁, forced expiratory volume in one second; FGF, fibroblast growth factor; FN, fibronectin; FVC, forced vital capacity; GA, gallic acid; GBA, gambogic acid; GC-MS, gas chromatograph-mass spectrometer; GCA, glycyrrhizic acid; GPx, glutathione peroxidases; GR, glutathione reductase; GSH, glutathione; HC, Houltuyenia cordata; HELFs, human embryonic lung fibroblast; HLF, human lung fibroblasts; HMGB1, high-mobility group box 1; HO-1, heme oxygenase-1; HPMECs, human pulmonary microvascular endothelial cells; HSM, Hirsutella sinensis mycelium; HSYA, hydroxy safflor yellow A; Hyp, hydroxyproline; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; IR, irradiation; Keap, Kelch like ECH-associated protein; LC3A/B, light chains 3A/B; LDH, lactate dehydrogenase; LOX, lipoxygenase; LPA1, lysophosphatidic acid receptor 1; LPO, lipid peroxide; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinases; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MFb, myofibroblasts; miR, miRNA; mKG, Modified Kushen Gancao Formula; MMP, matrix metalloproteinase; MPO, myeloperoxidase; NF- κ B, nuclear factor kappa B; NLRP, NOD-like receptor; NOX, NADPH oxidase; NQO1, NAD(P)H:quinone oxidoreductase 1; Nrf2, nuclear factor erythroid 2-related factor; NS, *Nigella sativa* L.; OM, Oxymatrine; OVA, ovalbumin; PARP, poly ADP-ribose polymerase; PDGF, platelet-derived growth factor; PF, pulmonary fibrosis; PG, prostaglandin; PMVEC, pulmonary microvascular endothelial cells; PQ, paraquat; p-Smads, phosphorylated Smads; PTX, paclitaxel; Res, resveratrol; ROS, reactive oxygen species; RPF, rapid pulmonary fibrosis; RPFs, Renshen pingfei decoction; SAA, salvanilic acid A; SARS, severe acute respiratory syndrome; SOD, superoxide dismutases; SP-D, surfactant protein-D; SY, safflor yellow; TAL, triterpene acids of loquat; Tan IIA, tanshinone IIA; T-AOC, total antioxidant capacity; TCM, traditional Chinese medicine; TGF- β 1, transforming growth factor- β 1; THP, tetrahydropalmatine; TIMP, tissue inhibitor of metalloproteinase; TNF- α , tumor necrosis factor- α ; TPL, triptolide; TQABDA, Tonifying Qi, Activating Blood and Dispersing Accumulation; VASH, Vasohibin; VEGF, vascular endothelial growth factor; XRT, x-ray treatment; YPF-G, total glycoside of Yupingfeng; α -SMA, α -smooth muscle actin

* Corresponding author.

E-mail addresses: liliuchengayd@163.com (L.-C. Li), kanliandi@163.com (L.-D. Kan).

<http://dx.doi.org/10.1016/j.jep.2016.12.042>

Received 12 September 2016; Received in revised form 9 December 2016; Accepted 26 December 2016

Available online 28 December 2016

0378-8741/© 2016 Elsevier Ireland Ltd. All rights reserved.

regulatory mechanisms, conduct standard clinical trials, and evaluate the possible side effects. The insights provided in present review will be needed for further exploration of botanical drugs in the development of PF therapy.

1. Introduction

Pulmonary fibrosis (PF) is a serious lung disorder characterized by excessive accumulation of extracellular matrix (ECM) (Wollin et al., 2015; Bardou et al., 2016). In the early period of PF, the affected lungs are mainly inflammatory cell infiltration, edema and congestion, and then converted to the injury of alveolar epithelial cells (AEC), abnormal proliferation of ECM-producing cells (mesenchymal cells including fibroblasts (FB) and myofibroblasts (MFb)), the overproduction of ECM (collagens, laminin, tenascin-C, etc.), resulting in progressive scarring and loss of lung function (Rajasekaran et al., 2015; Li et al., 2015a; Craig et al., 2015). Up to now, lots of studies have shown that the molecular mechanisms of PF is involved in the superabundant inflammation such as cytokines release and inflammasome activation (Hosseini et al., 2015), macrophages activation (Liu et al., 2016), FB to MFb transformation (Wollin et al., 2014), epithelial-mesenchymal transition (EMT), converting from epithelial phenotype to fibroblastic phenotype (Li et al., 2015a), matrix metalloproteinase (MMP)/(tissue inhibitor of metalloproteinase (TIMP)) balance (Zhou et al., 2016a), oxidative stress (Brass et al., 2016) and several signaling pathways activation (Chaudhary et al., 2007; Chen et al., 2016b) (Fig. 1). It is confirmed that one of the main pathological mechanisms of PF is the imbalance between the synthesis and degradation of ECM, while the degradation of ECM is mainly regulated by MMP and TIMP (Zhou et al., 2016a). The most components of ECM is degraded by MMP; TIMP is a primary inhibitor of MMP, while the overproduction of TIMP aggravates the fibrosis (Zhou et al., 2016a). During EMT, the down-regulated levels of epithelial markers (such as E-cadherin) and up-regulated levels of mesenchymal cells markers (such as α -smooth muscle actin (α -SMA), vimentin, N-cadherin, fibronectin (FN)) as well

as the signaling proteins transforming growth factor (TGF)- β 1, Smads, and phosphorylated Smads (*p*-Smads), are concomitant with the ability of epithelial cells to adopt mesenchymal phenotypes (Kolossova et al., 2011). Thus, the agents targeting these events may promote the development of PF treatment.

It is well known that the treatment options of lung fibrosis include the anti-oxidants, cytokine inhibitors, anti-fibrotic agents and lung transplantation or else (Prasad et al., 2016). However, these are confined to mostly focusing on one or two aspects in the process of lung injury and repair. The widely accepted therapeutic schedule for PF with the serial therapy of corticosteroids, immunosuppressive drugs plus anti-oxidants (N-acetylcysteine), may be no longer appropriate (Behr, 2013). Though pirfenidone has been demonstrated preferable activity for treating PF in clinical, it receives only a conditional recommendation for use and, the effectiveness and safety for long-time use is unknown yet (Papiris et al., 2012; Rogliani et al., 2016). Thus, further efforts are still urgently needed to develop novel strategies to prevent this refractory respiratory disease. Traditional Chinese medicine (TCM), one of the main parts of the medical practice, is just as a natural chemical library which produce synergistic effects through the synergistic mechanism, enhanced functions and less toxicity of the principle active ingredients (Boskabady and Farkhondeh, 2016; Gholamnezhad et al., 2016; Gu et al., 2016; Shakeri and Boskabady, 2015; Zhang et al., 2016). It often exerts wider action spectrum in managing the medical disorders either as mono-therapy or in combination with standard Western medical treatment (Chang et al., 2016; Lien et al., 2016; Yang et al., 2009; Zhang et al., 2016). Moreover, the single herbs and herbal formulations have provided a vast source for drug discovery such as Artemisinin (Tarning, 2016) and Berberine (Jin et al., 2016), in treating human

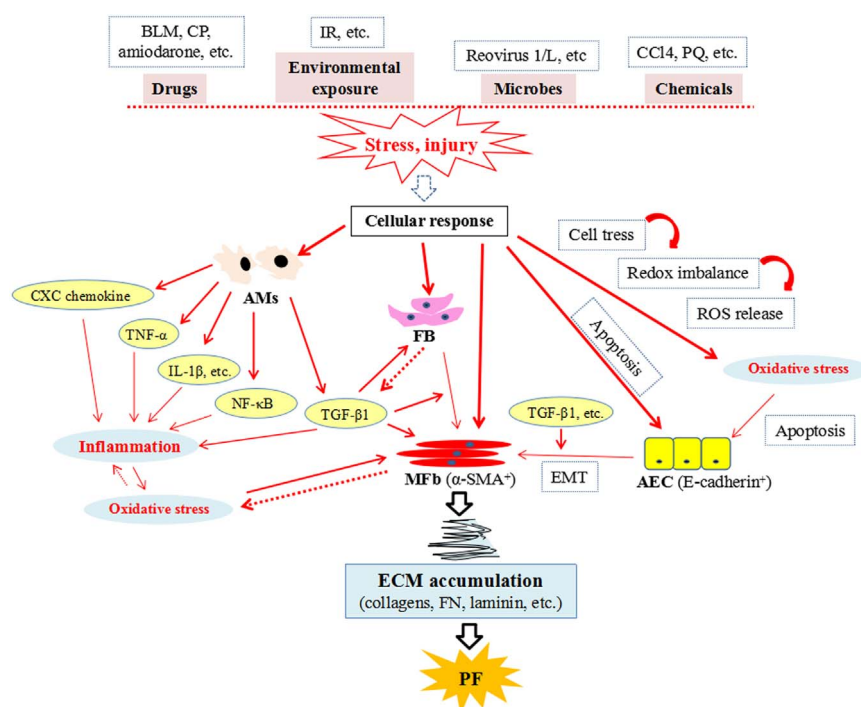


Fig. 1. The pathological mechanisms of pulmonary fibrosis. A series of factors (drugs, IR or else) trigger the continuous development of pulmonary fibrosis by inducing cell stress via superabundant inflammation, macrophages activation, abnormal FB proliferation, FB to MFb transformation, EMT and oxidative stress, resulting in excessive ECM accumulation and persistent fibrosis.

Table 1
The studies of single component from herbs for the therapy of PF.

Categories	Monomers	Herbal sources	Objects (model inducers, doses)		Ref.
			In vitro	In vivo	
Flavonoids	Baicalein	<i>Scutellaria baicalensis</i> Georgi	–	SD rats (BLM, 5 mg/kg), ICR mice (BLM, 3.5 mg/kg)	Tanno et al. (1988), Gao et al. (2013) and Hu et al. (2015)
	Tectorigenin	<i>Iris tectorum</i> Maxim.	–	SD rats (BLM, 7.5 U/kg)	Zhang, et al. (2010)
	Quercetin	<i>Leonurus sibiricus</i> L.	HELFS (SiO ₂ , 50 µg/ml)	SD rats (BLM, 5 U/kg)	Baowen et al. (2010) and Peng et al. (2013)
	HSYA	<i>Catharus tinctorius</i> L.	–	Wistar rats (1 g/L LPS and cigarette smoke)	Wang et al. (2014b)
Terpenoids	Triptolide	<i>Tripterygium wilfordii</i> Hook F.	MH-S AMs (IR, 2 Gy), NIH3T3 cells (TGF-β1, 5 ng/ml)	C57BL/6 mice (IR, 15 Gy)	Chen et al. (2016a)
	Celastrol	<i>Taxus brevifolia</i> Nutt.	–	Wistar rats (BLM, 3 U/kg)	Divya et al. (2016)
	Paclitaxel	<i>Eclipta prostrata</i> L.	A549, RLE-6TN AEC (TGF-β1, 5 ng/ml)	SD rats (BLM, 5 mg/kg)	Wang et al. (2013) and Zhou et al. (2016b)
	ESA	<i>Sabia miltiorrhiza</i> Bunge	–	ICR mice (BLM, 5 mg/kg)	You et al. (2015)
	Tan IIA	<i>Glycyrrhiza glabra</i> L.	FB 3T6	SD rats (BLM, 5 mg/kg)	Wu et al. (2014) and He et al. (2015)
	GCA	<i>Andrographis panicula</i> Nees	H22 cells	SD rats (BLM, 5 mg/kg)	Wang (2012) and Gao et al. (2015)
	Andro	–	–	Kunming mice (BLM, 15 mg/kg)	Guo et al. (2016)
	Paeoniflorin	<i>Paeonia lactiflora</i> Pall.	A549 AEC (TGF-β1, 2 ng/ml)	ICR mice (BLM, 5 mg/kg)	Ji et al. (2013) and Ji et al. (2016)
	Naringin	<i>Citrus paradisi</i> Macfad.	–	Kunming mice (PQ, 20, 30 or 50 mg/kg), Wistar rats (BLM, 5 mg/kg)	Chen et al. (2013b) and Turgut et al. (2016)
	Salidroside	<i>Rhodiola rosea</i> L.	A549, rat AEC (TGF-β1, 5, 10 ng/ml)	SD rats (BLM, 5 mg/kg)	Tang et al. (2016)
Astragalin	<i>Diospyros kaki</i> L.f.	BEAS-2B cells (H ₂ O ₂ , 20 µM)	BALB/c mice (OVA, 20 µg)	Cho et al. (2015)	
Phenols	Resveratrol	<i>Reynoutria japonica</i> Houtt.	–	Wistar rats (BLM, 2.5 mg/kg), ICR mice (LPS, 5 mg/kg)	Akgedik et al. (2012) and Zhang et al. (2015)
	Curcumin	<i>Curcuma longa</i> L.	PMVEC, primary FB (IR, 2 Gy)	C57BL/6 mice (0.5 µg LPS or 13.5 Gy IR), CBA/J mice (reovirus 1/L, 10 ⁷ PFU)	Lee et al. (2010), Smith et al. (2010), Avasarala et al. (2013) and Jiang and Zhang (2015a)
	EGCG	<i>Camellia sinensis</i> (L.) Kuntze	FB W1-38 (TGF-β1, 10 ng/ml)	Wistar rats (BLM, 6.5 U/kg), SD rats (IR, 22 Gy)	Sriram et al. (2009a, 2009b, 2015) and You et al. (2014)
	Corilagin	<i>Caesalpinia coriaria</i> (Jacq.) Willd.	–	BALB/c mice (BLM, 1 mg/ml)	Wang et al. (2014c)
	Galic acid	<i>Areca catechu</i> L.	–	Wistar rats (BLM, 7.5 U/kg)	Nikhakht et al. (2015)
	SAAs	<i>Sabia miltiorrhiza</i> Bunge	FB 3T6	Wistar rats (BLM, 5 mg/kg)	Pan et al. (2014)
	SAB	–	FB MRC-5 (TGF-β1, 10 ng/ml)	–	Zhang et al. (2014b)
	Nefertine	<i>Nelumbo nucifera</i> Gaertn.	RAW264.7 cells (BLM, 1 µg/ml)	Kunming mice (0.1 mg BLM per mouse or 6.25 mg/kg amiodarone)	Zhao et al. (2010) and Niu et al. (2013a)
	Isolensinine	<i>Corydalis yanhusuo</i> W.T.Wang	–	Kunming mice (BLM, 0.1 mg per mouse)	Xiao et al. (2005)
	THP	–	–	SD rats (IR, 15 Gy)	Yu et al. (2016)
Other monomers	Oxymatrine	<i>Sophora flavescens</i> Ait.	–	C57BL/6 mice (BLM, 3 mg/kg)	Liu et al. (2012)
	Osthole	<i>Cnidium monnieri</i> (L.) Cusson	–	SD rats (BLM, 5 mg/kg)	Hao and Liu (2016)
	GBA	<i>Garcinia hanburyi</i> Hook.f.	A549 AEC, HPMECs, FB HLF-1 (5 ng/ml TGF-β1, 100 µM CoCl ₂ or 2% O ₂)	SD rats (BLM, 5 mg/kg)	Qin et al. (2016)
	–	–	–	–	–

AEC: alveolar epithelial cells; AMs: alveolar macrophages; Andro: Andrographolide; BLM: bleomycin; CCl₄: carbon tetrachloride; CP: cyclophosphamide; EGCG: epigallocatechin-3-gallate; ESA: edipia saponin A; ET: endothelin; FB: fibroblasts; GCA: glycyrrhizic acid; HELFS: human embryonic lung fibroblast; HLF: human lung fibroblasts; HPMECs: human pulmonary microvascular endothelial cells; HSYA: hydroxy safflor yellow A; IR: irradiation; LPS: lipopolysaccharide; MFB: myofibroblasts; PF: pulmonary fibrosis; PMVEC: pulmonary microvascular endothelial cells; PQ: paraquat; SAA: salivianic acid A; Tan IIA: tanshinone IIA; TGF-β1: transforming growth factor-β1; THP: tetrahydropalmatine

diseases.

Recently, emerging researches have been conducted to investigate the efficacy of TCM in the treatment of PF. With regard to the applied *in vivo* PF models, bleomycin (BLM) remains the most used experimental tool to evaluate the pathogenetic mechanisms and new therapeutic approaches for acute lung injury and fibrosis, including the exploration of TCM (White et al., 2016; Cabrera et al., 2015; Scotton et al., 2013). It has been proven that the active agents from TCM, in particular, the flavonoids, terpenes and alkaloids, exhibit potential benefits for PF, the biological effects of which appear to involve the regulation of inflammation, oxidant stress, and pro-fibrotic signaling pathways. Here, we highlight the recent advances of the anti-fibrotic agents from TCM in the prevention of PF and their proposed biological effects, and summarize future perspectives on such work, hoping to provide a promising view in the discovery of the anti-fibrotic compounds from further evaluation and application of TCM in the management of PF.

2. Methods

The literature materials were obtained from the scientific databases including the Pubmed, SpringerLink, Web of Science and CNKI databases (up to Aug 2016), and was to identify the studies on the anti-fibrotic role of the active agents from TCM as well as the possible mechanisms. The search keywords for these work included “lung fibrosis” or “pulmonary fibrosis”, and “traditional Chinese medicine”, “extract” or “herb” in all fields. The names of the chemical components listed in present review are corresponding to that in the journal plant list. In a broader viewpoint, insights gained from these work can serve in expanding and improving the utilization of TCM in the development of PF treatment.

3. Single component from herbs for the therapy of PF

Currently, emerging herbal medicines have been available for clinical therapy in diverse human diseases, even the single herb-derived agents that are widely used (e.g. taxol and flavoxate). It is reported in the ethnopharmacological studies that the single component from herbs have been proven possessing potential benefits in PF treatment, particularly, the monomers which belong to flavonoids, terpenes and alkaloids (Table 1).

3.1. Flavonoids

Baicalein (BAI) is a natural plant flavone that exhibits various biological activities. BAI (0.1–100 μ M) could inhibit the oxidative and arachidonate metabolism of alveolar macrophages (AMs) which were from the bronchoalveolar lavage of patients with PF (Tanno et al., 1988). In a rat model, orally administered daily with BAI (50, 100 mg/kg) from day 1–28 after BLM exposure lowered the degree of PF, remarkably decreased the levels of Hyp (the main element of collagens), α -SMA (a MFb marker protein), miRNA (miR)-21, TGF- β 1 and p-Smad2/3, but the total antioxidant capacity (T-AOC, an antioxidant indicator) was higher than in those without BAI treatment (Gao et al., 2013). Further evidence showed that BAI treatment not only entirely restored the normal liver lipid profile, but also greatly improved the fat abundance and composition in an animal model induced by BLM, but not with dexamethasone, a commonly used glucocorticoids for treatment of PF (Hu et al., 2015). These protective effects might be achieved by repressed inflammation, improved antioxidant activity, miR-21 function and TGF- β /Smad signaling pathway, as well as fewer adverse effects on liver lipid disorder (Gao et al., 2013; Hu et al., 2015; Tanno et al., 1988). Nevertheless, more researches are still needed to present its anti-fibrotic effects including the studies on different *in vitro* and *in vivo* models as well as the lacked clinical trials.

Tectorigenin is a type of O-methylated isoflavone. It significantly

inhibited the proliferation of lung FB in BLM-treated rats (Zhang, et al., 2010). Moreover, tectorigenin remarkably enhanced miR-338* expression of lung FB and down-regulated the levels of FB matrix proteins procollagen type 1 α 1 (COL1A1) and FN, and lysophosphatidic acid receptor 1 (LPA1), which is involved in many biological responses such as cell differentiation and apoptosis. This indicates a potential inhibitory role of tectorigenin on the pathogenesis of PF, however, there is scarcely any data related to its role in lung patients.

Quercetin is also a flavonoid found in a wide variety of plants that presents wide ranges of biological activities. It was clinically observed that frequent intake of quercetin-rich foods was inversely associated with the risk of lung cancer patients (Lam et al., 2010). To evaluate the preventative effects of quercetin on BLM-induced PF *in vivo*, liposomal quercetin was intravenously injected 1 day prior to BLM administration and continued to the end of the study (for 4 weeks) (Baowen et al., 2010). As a result, the increased macrophage counts, and the neutrophil and lymphocyte counts in bronchoalveolar lavage fluid (BALF) were diminished both on day 7 and 14 in liposomal quercetin treated group compared with BLM-induced group (Baowen et al., 2010). Meanwhile, the levels of tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , and IL-6 in BALF at day 7 were strikingly reduced after liposomal quercetin treatment. Moreover, treatment with liposomal quercetin apparently lessened the PF areas and collagen deposition accompanied with decreased TGF- β 1 expression by histopathological assessment. However, the histopathological assessment and cell counts in BALF showed that there were no significant differences between liposomal quercetin-treated and BLM model groups when applying late therapeutic strategies with administrated liposomal quercetin after BLM being intratracheally injected for 7 days. It suggested that the main role of liposomal quercetin was on reducing the initial injury responses triggered by BLM, but not the level of fibrosis after the proinflammatory responses occurred and developed (Baowen et al., 2010). In another study of human embryonic lung fibroblasts (HELFS) which were incubated with the cultured supernatant of AMs that collected from the BALF of PF patients, quercetin (20, 40 μ mol/L) could significantly reverse the decreased MMP-1 expression and increased TIMP-1 production that induced by SiO₂ (Peng et al., 2013). These data show that quercetin may provide a strategy for protecting PF patients but more clinical studies is still needed.

Safflor yellow (SY) is the aqueous extract of safflower (*Carthamus tinctorius* L.) and its injection has been used to treat myocardial ischemia in the clinical of China for many years. Hydroxy safflor yellow A (HSYA) is the bioactive ingredient of SY and safflower. It has been reported effective to treat acute cerebral infarction patients (Li et al., 2014a). Further study investigated the effect of HSYA on small airway remodeling in a rat model induced by cigarette smoke and lipopolysaccharide (LPS) (Wang et al., 2014b). HSYA was reported to significantly attenuate the thickening and collagen deposition of the small airway and inhibit TGF- β 1 protein expression and phosphorylation of p38 mitogen-activated protein kinases (MAPK, involves the production of pro-inflammatory and pro-fibrotic mediators) in the lung tissue of rats, indicating the potential benefit of HSYA on attenuating the pathological airway remodeling (Wang et al., 2014b). However, no direct role of HSYA on PF patients is shown yet.

3.2. Terpenoids

Triptolide (TPL) is a diterpenoid epoxide. Previous clinical trials evaluated that TPL in combination with procaterol and theophylline is effective for the treatment of steroid-resistant asthma (Jiang et al., 2006). Lately, other authors established an irradiation (IR)-induced PF in C57BL/6 mice with 15 Gy on whole chest and then the mice were treated without or with TPL (*i.v.* 0.25 mg/kg, qod for 1 month) (Chen et al., 2016a). It demonstrated that TPL effectively reduced the IR-induced PF as evidenced by the less MFb, collagen deposition, ROS, and infiltrated AMs in the IR-lung tissue, as well as declined levels of

NADPH oxidase (NOX)-2 and NOX-4 in AMs (Chen et al., 2016a). Its potential role in PF patients is encouraged to be included in the ongoing studies.

Celastrol is a quinone-methide tri-terpenoid which is derived from *Tripterygium wilfordii* Hook F. It was observed that BLM (3 U/kg bw)-induced rats exhibited morphological abnormalities with decreased levels of enzymatic antioxidants (superoxide dismutases (SOD), catalase (CAT), glutathione peroxidases (GPx), glutathione reductase (GR)) and non-enzymatic antioxidants (glutathione (GSH), Vitamin C and E), nonetheless, above conditions were prominently suppressed upon celastrol (5 mg/kg) treatment (Divya et al., 2016). In addition, celastrol treatment enhanced the expression of nuclear factor erythroid 2-related factor (Nrf2) and heme oxygenase-1 (HO-1), but decreased the activities of MMP2 and MMP9, count of mast cells, and levels of TNF- α , histamine and serotonin. These observations support that celastrol protects against BLM-induced PF by inhibiting inflammation and enhancing antioxidant ability which probably through the activation of Nrf2. Celastrol therefore potentially be used as an anti-fibrotic agent, but it has not been appeared or used in the studies of human diseases.

Paclitaxel (PTX) is a complex diterpene alkaloid. PTX and carboplatin combination chemotherapy was shown effective and safe in advanced non-small cell lung cancer patients (Minegishi et al., 2011). Wang and colleagues investigated the anti-fibrotic effect of the low-dose PTX (10–50 nM *in vitro*, and 0.6 mg/kg *in vivo*) (Wang et al., 2013). This research showed that PTX treatment resulted in the amelioration of BLM-induced PF in rats with reduction of lung index and collagen deposition. Besides, PTX treatment resulted in EMT phenotypic reversion and normalization of vimentin, E-cadherin, Smad3 and p-Smad3 expression, while A549 AEC treated with PTX, in majority, were resistant to the TGF- β 1-induced EMT, whereas PTX-untreated controls are more vulnerable to EMT. Through decreasing Smad3/p-Smad3 expression and up-regulating miR-140, PTX treatment could significantly reverse the EMT of AEC and prevent PF of rats, demonstrating the suppression of TGF- β 1/Smad3 pathway *via* up-regulating miR-140 with low-dose PTX in preventing PF (Wang et al., 2013). A recent study declared that PTX liposome inhalation in rats, could improve survival rate and PF Ashcroft score, and decreased the thickness of the alveolar interval as well as the levels of collagen type I (Col-I) and III and TGF- β 1 expression (Zhou et al., 2016b). Thus, the clinical attempt of PTX in PF may be a meaningful practice for the development of new drugs.

Eclipta prostrata L. is considered as a nourishing herbal medicine with pleiotropic effects. In a Chinese medical practice report with 50 patients, a large dose of fresh *Eclipta prostrata* L. in combination with a small amount of the peels from *Citrus reticulata* Blanco has a good curative effect on the treatment of chronic bronchitis patients (Li et al., 2004). You et al. (2015) recently carried out a research of *Eclipta prostrata* extract (EXT, 2.5, 1.25, 0.625 g/kg, oral) and one of its main triterpene glycosides component eclipta saponin A (ESA, 80 mg/kg, oral) on BLM-induced mice model. The authors declared that EXT treatment not only ameliorated BLM-induced lung pathological changes, weight loss, mortality, and lung index, but also evidently reduced the lung Hyp and malondialdehyde (MDA, an indicator of lipid peroxidation) content, alleviated the levels of cyclooxygenase (COX)-2, TGF- β 1, MMP-2 and α -SMA, as well as elevated the ratio value of MMP-9/TIMP-1, enhanced the lung SOD activity (You et al., 2015). Besides, the survival rate, loss of body weight and lung index were not significantly improved by ESA administration, but the Hyp level and the score of inflammation and fibrosis in lung tissue were significantly reduced after 14 days treatment with ESA at the same dose. ESA could also block the up-regulated expression of TGF- β 1 and α -SMA induced by BLM for 28 days. These data show that *Eclipta prostrata* has protective effects against PF induced by BLM possibly *via* reducing oxidative stress, tissue inflammation, and the subsequent EMT, which may be involved with the triterpenoid saponins, such as ESA.

Tanshinone IIA (Tan IIA) is an important lipophilic diterpene. It has been clinically proven effective in treating the patients with liver fibrosis (Niu et al., 2013b) and severe pneumonia (Xiao et al., 2016). Wu et al. (2014) provided further evidence that Tan IIA treatment notably decreased the expression of TGF- β 1, reversed the reduced production of angiotensin converting enzyme (ACE)-2 and its enzymatic product angiotensin (ANG)-(1–7) in rats' lungs induced by BLM. It indicates the protective effects of Tan IIA on experimental PF may also ascribe to regulate the ACE-2/ANG-(1–7) axis, which plays a key negative regulatory factor for patients with severity of lung edema (Kuba et al., 2005) and acute lung failure (Imai et al., 2005). Subsequently, treatment with Tan IIA markedly attenuated the severe lung edema, inflammation and fibrosis in the BLM-treated rats with significantly decreased counts of total cells, neutrophils and lymphocytes in BALF (He et al., 2015). In addition, BLM-induced increased expression of TNF- α , IL-1 β , IL-6, COX-2, prostaglandin (PG) E2, malondialdehyde (MDA, an indicator of lipid peroxidation), iNOS and NO in rats was also suppressed by Tan IIA injection. This demonstrates that Tan IIA reduces BLM-induced inflammatory cell infiltration, pro-inflammatory cytokine release and excessive collagen deposition in rats, while the exerted effect may be *via* modulating NO production during the development of PF (He et al., 2015). These clinical and pre-clinical contribution of Tan IIA should drive future efforts on PF patients.

Glycyrrhizic acid (GCA) has been demonstrated by modern scientific approaches to possess a wide spectrum of pharmaceutical properties, such as anti-inflammatory, anti-diabetic, anti-oxidant, anti-tumor, anti-microbial, and anti-viral properties (Ming and Yin, 2013). From a work with 42 cases of PF patients, intravenous drip with GCA diamine (300 mg daily for 4 weeks) in combination with its capsules (150 mg daily for another 5 months) could significantly reduce the serum levels of hyaluronic acid and procollagen III along with slight adverse reactions (edema, heart palpitations, increased blood pressure) in PF patients, when compared to those treated with prednisone (0.5 mg/kg daily for 4 weeks and 0.125 mg/kg daily for another 5 months) (Wang, 2012). Recent experimental study revealed that GCA treatment (50, 100, 200 mg/kg bw/d) could ameliorate BLM-induced local fibrotic lesions and lung edema with mild thickening of the lung interstitium, remarkably reduced the areas of collagen deposition (by Masson staining) and the contents of Col-I and Hyp in the lung in a dose-dependent manner (Gao et al., 2015). Following 28-days GCA treatment, BLM-induced increases of inflammatory cell counts, elevated levels of total protein and various inflammatory cytokines such as TNF- α , IL-1 β and IL-6 in BALF were markedly reduced. Meanwhile, GCA treatment (100, 200 mg/kg bw/d) significantly inhibited BLM-induced elevation of myeloperoxidase (MPO; a marker of neutrophil influx and oxidative stress), MDA, TGF- β 1, p-Smad2, p-Smad3, and mesenchymal cell markers (α -SMA, FN and vimentin), accompanied by down-regulation of AEC marker (E-cadherin) in the lungs (Gao et al., 2015). *In vitro* by employing a murine fibroblast cell line 3T6, GCA could lead to the down-regulated expression of ECM degradation proteins (MMP-3, MMP-7, MMP-8 and MMP-9), anti-apoptotic protein Bcl-2 and cell cycle regulatory proteins (Cyclin B1, Cyclin D1 and Cyclin E) along with up-regulated pro-apoptotic protein Bax and G1 check-point proteins (P53 and P21), as well as the executors of apoptotic events (cleaved caspase-3, cleaved caspase-9 and cleaved poly ADP-ribose polymerase (PARP)) (Gao et al., 2015). It also demonstrated that GCA significantly suppressed the migration and invasion of 3T6 cells by scratch wound assay and Transwell assay. It demonstrate that GCA owns the activity to ameliorate BLM-induced PF, inflammation, oxidative stress, EMT and activation of TGF- β signaling pathway, suppress the proliferation and migration of FB, and promote FB apoptosis.

Andrographolide (Andro), an active diterpenoid labdane component extracted from *Andrographis panicula*, is generally prescribed for treatment of inflammatory associated diseases, including asthma, laryngitis and upper respiratory tract infection (Jayakumar et al.,

2013). It has shown that Andro sulfonate nebulization could improve the life quality scores, blood gas indexes and forced expiratory volume in one second (FEV1) percentage of predicted value in treating acute exacerbation of chronic obstructive pulmonary disease (COPD) patients (Chen and Liu, 2013). A recent work has explored the enhanced anti-tumor activity and reduced toxicity by combination Andro and BLM in the established ascitic tumor-bearing mice model that induced by intraperitoneal injected with H22 hepatoma cells (2×10^6 cells/mouse) (Guo et al., 2016). The study indicated that BLM combined with Andro was significantly more effective than BLM alone on inhibiting the tumor growth, arresting the cell cycle at G0/G1 phase, promoting the capase-3 and -8 activity to induce cancer cell apoptosis, which may be related to the transcriptional regulation of P53/P21/Cyclin pathways. Moreover, BLM induced PF in tumor-bearing mice, but BLM combined with Andro dramatically alleviated the lesion in PF by activating the SOD, suppressing MDA and Hyp production, meanwhile, attenuating the IL-1 β , TNF- α , IL-6 and TGF- β 1 level (Guo et al., 2016). These events were associated with the effect of Andro on the inhibition of protein expression of TGF- β 1, α -SMA, p-Smad2/3, and enhanced expression of Smad7. Thus, Andro could improve BLM-based chemotherapy by both enhancing BLM tumoricidal effect and reducing BLM-associated side-effects, which maybe mediated by effecting cell cycle and apoptosis on tumor cells, and weakening the inflammation and collagen over-production in BLM-induced PF (Guo et al., 2016). It renders that Andro might be a promising adjuvant therapeutic agent with the combination of BLM in cancer chemotherapy and worthy of further synergistic study in clinical.

3.3. Glycosides

Paeoniflorin, a monoterpene glucoside, is the main active constituent extracted from the dry roots of *Paeonia lactiflora* Pall., which is extensively used in China for more than 1000 years to treat numerous diseases including patients with terminal cancer (Xu et al., 2016). In mice treated with BLM, paeoniflorin (50 mg/kg) significantly prolonged the survival periods, attenuated the inflammatory cells infiltration, interstitial fibrosis, and ECM deposition, decreased the contents of Hyp, Col-I and α -SMA as well as the expression of TGF- β 1, Smad4 and p-Smad2/3 in lung tissues (Ji et al., 2013). Moreover, paeoniflorin increased Smad7 expression and interferon (IFN)- γ content, but only slightly affected the mRNA expression of MMP-1 and TIMP-1 in lung tissue of mice. The therapeutic potential for the treatment of BLM-induced PF mainly by suppressing ECM deposition in lung tissue through reducing the synthesis of Col-I by inhibiting the activation of TGF- β /Smad pathway and increasing the expression of IFN- γ (Ji et al., 2013). Recently, it was found that TGF- β 1-induced EMT, shown by changed cell morphology, increased cell migration, up-regulated vimentin and α -SMA expression, and Col-I and Col-III levels with decreased E-cadherin expression, were repressed by the co-incubation with paeoniflorin in A549 cells (Ji et al., 2016). Moreover, paeoniflorin could dose-dependently attenuate TGF- β 1-induced expression of Snail (a major transcription factor governing EMT) and p-Smad2/3, markedly increased Smad7 level, but slightly affected the activation of p38 MAPK in A549 cells (Ji et al., 2016). These results provide further evidence that paeoniflorin suppresses the early stages of TGF- β mediated EMT in AEC, likely by decreasing Snail expression via a Smad-dependent pathway. These data provide the laboratory evidence of paeoniflorin in treating patients with PF.

Naringin (4',5,7-trihydroxy-flavonone-7-rhamnoglucoside) is a well-known flavanone glycoside with a strong oxygen radical scavenger by rapid donation of hydrogen atom to radicals (Rajadurai and Prince, 2006). The investigators had previously found the significant inverse associations between lung cancer risk and the main food sources of naringin (white grapefruit) after adjusting for smoking and intakes of saturated fat and beta-carotene (Le Marchand et al., 2000). In a mice model with paraquat (PQ, 50 mg/kg, *i.p.*)-induced acute lung injury

(ALI) and PF, daily treatment with naringin increased the survival rates of mice within 7 days (Chen et al., 2013). In addition, naringin treatment significantly reduced PQ (20 mg/kg, *i.p.*)-induced up-regulation of TNF- α , TGF- β 1, MMP-9 and TIMP-1, levels of pulmonary MDA and Hyp, while increased the activities of enzymatic antioxidants including SOD, GSH-Px and HO-1, suggesting that it may be a potential therapeutics for management of PQ intoxication via alleviating oxidative stress, regulating TGF- β 1 activity and MMP-9/TIMP-1 ratio, and reducing the collagen fibers deposition (Chen et al., 2013). Turgut and coworkers recently published a work of naringin on BLM (5 mg/kg; via the tracheal cannula)-induced PF in rats (Turgut et al., 2016). The authors announced that naringin (80 mg/kg) administration led to a significant decrease in thin lined alveolar septa, inflammatory cell infiltration, Ashcroft quantitative pathological scoring, and mast cell recruitment compared with the BLM group; moreover, it markedly decreased the rats' lung index and increased body weight, reduced TNF- α and IL-1 β activities, Hyp content, and MDA level, while increased GPx and SOD activities (Turgut et al., 2016). The protective effects of naringin on lung cancer patients and experimental PF may be due to its potential of preventing the formation of oxygen free radicals, reducing inflammatory cytokine levels, and/or removing them from the medium and also its antioxidant nature, which may also benefit human suffers.

Salidroside, isolated from *Rhodiola rosea* L., is a phenolic glycoside and has long been used as a medicinal herb to prevent high altitude sickness in China. It was seen that salidroside could protect against epirubicin-induced early left ventricular regional systolic dysfunction in patients with breast cancer (Zhang et al., 2012). Surprisingly, salidroside has also been reported to protect against PF in a recent work (Tang et al., 2016). It was reported that salidroside attenuated BLM-triggered structure distortion, collagen overproduction, excessive inflammatory infiltration, and pro-inflammatory cytokine release, and oxidative stress damages in lung tissues (Tang et al., 2016). In addition, salidroside inhibited the levels of p-IkBa, p-Smad2/3, TGF- β 1, vimentin, FN, α -SMA, and nuclear factor kappa B (NF- κ B) p65 nuclear accumulation, while up-regulated E-cadherin level and activated Nrf2-antioxidant signaling in BLM-treated lungs. Besides, salidroside was capable of reversing the recombinant TGF- β 1-induced EMT-like changes in human A549 cells and primarily cultured rat AEC *in vitro* (Tang et al., 2016). Collectively, salidroside may drive new drugs in protecting against fibrotic lung diseases. More studies are needed to confirm and increase the clinical application of these results.

Astragaln, kaempferol-3-O-glucoside from leaves of persimmon and green tea seeds, has been used to elucidate its effects on oxidative stress-induced airway epithelial BEAS-2B cells by H₂O₂ and OVA-sensitized BALB/c mice (Cho et al., 2015). It reported that exposure of 20 μ M H₂O₂ accelerated E-cadherin loss and vimentin induction, increased Col-I production in airway epithelial BEAS-2B cells, which was reversed by non-toxic astragaln. Astragaln also reduced the collagen fiber deposition, airway tissue levels of ROS and vimentin enhanced by OVA challenge (Cho et al., 2015). Furthermore, astragaln blocked H₂O₂-induced expression of the autophagy-related beclin-1 and light chains 3 A/B (LC3A/B) in BEAS-2B cells and OVA-challenged airway subepithelium. Meanwhile, the induction of autophagy by spermidine influenced the epithelial induction of E-cadherin and vimentin that was blocked by treating astragaln. These results demonstrate that astragaln was effective in ameliorating oxidative stress-associated PF through disturbing airway EMT and epithelial autophagic stress. However, little is known about its role in clinical.

3.4. Phenols

Resveratrol (Res), trans-3,5,4'-trihydroxystilbene, a natural plant polyphenol that mainly found in some plant species, has been proven to improve the lung functions of COPD patients and reduce inflammatory biomarkers in patients with nonalcoholic fatty liver disease

(Faghihzadeh et al., 2014; Liu et al., 2015). The authors carried out a study using the first oral dose of Res (10 mg/kg) to the male Wistar albino rats just after 14 days of intratracheal BLM exposure and continued until sacrifice on 29th day (Akgedik et al., 2012). The data showed that Res administration markedly decreased the counts of total cells and neutrophils in BALF, reduced the levels of Hyp (in lungs) and MDA (in lungs and serum), while increased the levels of T-AOC (in lungs and serum) when compared to BLM rats. However, Res could slightly reduce the increment of fibrosis score that BLM triggered, although it was not reached at statistically significant level. This preclinical study indicated that the treatment of Res at a dose of 10 mg/kg when administered in the late post BLM period (14 days after BLM) suppressed, at least in part, the lung fibrosis induced by BLM exposure in rats (Akgedik et al., 2012). Further study reported a role of Res (injected intraperitoneally at 0.3 mg/kg once daily) on LPS (a single intratracheal dose of 5 mg/kg)-induced changes of EMT and PF during a 28-days period in male ICR mice (Zhang et al., 2015). The authors found that 28 days with Res treatment not only markedly attenuated LPS-induced extensive deposition of fibrillar collagen and the destruction of normal pulmonary architecture, but also decreased TGF- β 1 production, Smad2/Smad3 phosphorylation and Smad4 expression, and reversed EMT as evidenced by the increased E-cadherin and decreased α -SMA levels. Moreover, Res therapy for 28 days significantly attenuated the MDA level, increased the levels of T-AOC, CAT and SOD in lung tissue of LPS-evoked mice (Zhang et al., 2015). These data suggest that inhibition of TGF- β 1/Smad activation and EMT may contribute to the protection against LPS-induced PF afforded by Res. Further clinical evidence is necessary to confirm its role in PF.

Curcumin, a natural phytochemical present in turmeric, has been shown to play a major role in various chronic diseases, including cardiovascular, pulmonary, autoimmune and neoplastic diseases (Aggarwal and Harikumar, 2009). It also showed that curcumin effectively inhibited the proliferation (1–20 μ M curcumin) and collagen secretion (5, 10 μ M curcumin in the absence or presence of 6 ng/ml TGF- β) of lung FB from PF patients in a dose-dependent manner (Smith et al., 2010). Curcumin also boosted antioxidant defenses by increasing HO-1 levels in the isolated mouse pulmonary microvascular endothelial cells (PMVEC) and primary FB, and blocked radiation-induced generation of ROS (Lee et al., 2010). In addition, the Hyp level in irradiated lungs was evidently lower, and the survival rate and HO-1 level in lungs were elevated in mice fed the 5% (w/w) curcumin diet, whereas curcumin supplementation did not affect tumor response to radiation. Moreover, 1% curcumin significantly decreased TNF- α level in BALF from LPS-challenged mice; the decrease was more pronounced when curcumin was given at a dose of 5% (Lee et al., 2010). Using the model of reovirus 1/L-induced acute viral pneumonia which displays many characteristics of human acute respiratory distress syndrome (ARDS)/ALI, female CBA/J mice were treated with curcumin (50 mg/kg) 5 days prior to intranasal inoculation with 10^7 PFU reovirus 1/L and daily, thereafter (Avasarala et al., 2013). The study showed that curcumin treatment *in vivo* effected both inflammatory (diffuse alveolar damage) and fibrotic lesion development leading to a significant reduction in the development of ALI/ARDS in reovirus 1/L-infected mice, potentially *via* the modulation of cytokine/chemokine expression through the NF- κ B pathway as well as the host fibrotic response during the regeneration phase of the disease through modulation of the TGF- β pathway (Avasarala et al., 2013). In a clinical study directly on PF patients with paraquat poisoning, curcumin (oral, 1 g/kg day) in combination with conventional therapy could more significantly prolong the survival time of patients, reduce the levels of MMP-9 and TIMP-1, and attenuate the degree of PF than those of the only conventional therapy group, but cannot reduce the mortality rate (Jiang and Zhang, 2015a). These work indicate that curcumin may be an attractive new agent in the treatment of PF.

Epigallocatechin-3-gallate (EGCG), a kind of polyphenols of green tea, has been studied for its anti-oxidative (Higdon and Frei, 2003) and

anti-fibrotic properties (Sriram et al., 2009a, 2009b, 2015; You et al., 2014). Upon EGCG (20 mg/kg) treatment, BLM-triggered increased level of Hyp and activities of pathophysiological enzymes such as aspartate transaminase, alanine transaminase, lactate dehydrogenase (LDH) and alkaline phosphatase were attenuated in Wistar rats (Sriram et al., 2009b). BLM-induced rise in the level of glycoconjugates and activities of matrix degrading lysosomal enzymes in lungs and serum were reduced upon EGCG supplementation along with attenuated BLM-induced ultrastructural changes as observed from transmission electron microscopy studies (Sriram et al., 2009b). Furthermore, the levels of ROS, lipid peroxide (LPO), histamine and serotonin, the activity of MPO, and the expression of NF- κ B, TNF- α and IL-1 β , were increased due to BLM challenge, however, they were significantly reduced on EGCG treatment (Sriram et al., 2009a). It also showed increased inflammation and alveolar damage by histopathological analysis and accumulated collagen deposition by picrosirius red staining in BLM-challenged rats that were decreased upon EGCG treatment (Sriram et al., 2009a). In addition, the declined activities of SOD, CAT, GSH, GST and NAD(P)H: quinone oxidoreductase 1 (NQO1) in BLM-injured rats were restored upon EGCG treatment (Sriram et al., 2009a). EGCG also induced Nrf2 expression, but had no significant change on the expression of Kelch like ECH-associated protein (Keap)-1, a vital factor in Nrf2 signaling cascade. It indicates Nrf2-Keap1 signaling involves EGCG enhanced anti-oxidant activities and Phase II enzymes with subsequent restraint inflammation during BLM-induced PF (Sriram et al., 2009a). Recently, Sriram and partners published additional data of the effects of EGCG focused on regulating FB activation and TGF- β 1 signaling (Sriram et al., 2015). In the rat model, EGCG treatment normalized the BLM induced significant elevation of MMP-2 and -9 expression, increased RNA and protein expression of TGF- β 1, Smads and α -SMA (Sriram et al., 2015). *In vitro*, simultaneous treatment of EGCG to FB (WI-38 cells) significantly decreased the increase of FB proliferation, Hyp level, and protein expression levels of p-Smad, α -SMA and Col-I, alongside normalizing the MMPs expression upon TGF- β 1 incubation (Sriram et al., 2015). It revealed that EGCG inhibited FB activation and collagen accumulation by inhibiting TGF- β 1 signaling and thus may be effective agent against PF. Not surprisingly, treatment with EGCG (intraperitoneally injection; 25 mg/kg) daily for 30 days also exerted protective role on irradiation-induced PF in rats using a dose of 22 Gy (You et al., 2014). The study declared that EGCG treatment reduced irradiation-induced rat mortality rates and improved histological changes in the lung, lessened collagen depositions, MDA content, and serum levels of TGF- β 1, IL-6, and IL-10, while activated Nrf-2, HO-1, and NQO-1 (You et al., 2014). Lately, a phase II trial confirmed that EGCG (oral, 440 μ mol/L) is effective and safe to treat acute radiation-induced esophagitis in patients with stage III lung cancer with depressed radiation therapy oncology group score and pain score (Zhao et al., 2015a). Collectively, blockage of several key events in experimental lung fibrosis and the inhibitory role in lung cancer render EGCG as a promising anti-fibrotic agent for PF.

Corilagin, which is discovered in a number of medicinal plants such as *Caesalpinia coriaria*, has shown anti-fibrotic properties in treating PF (Wang et al., 2014c). It was shown to reduce the number of apoptotic lung cells and prevent lung epithelial cells from membrane breakdown, effluence of lamellar bodies and thickening of the respiratory membrane through a transmission electron microscopy 24 h after aerosol BLM (1 mg/ml) exposure (Wang et al., 2014c). Moreover, BLM-triggered expression of MDA, IKK α , p-IKK α , NF- κ B P65, TNF- α and IL-1 β , and reduced expression of I- κ B in mice lung tissue or in BALF, were reversed by high-dose corilagin (100 mg/kg *i.p.*) more dramatically than by low dose (10 mg/kg *i.p.*). Corilagin also inhibited TGF- β 1 production and α -SMA expression in lung tissue. This finding provides evidence that corilagin attenuates lung injury and fibrosis as a consequence of BLM inhalation, which is attributed to its anti-oxidative, anti-inflammatory activities, as well as inhibition of NF- κ B

and TGF- β 1 signaling (Wang et al., 2014c). Corilagin may be a promising anti-fibrotic agent but warrants further studies.

Gallic acid (GA; 3,4,5-trihydroxybenzoic acid) and its derivatives are considered the main polyphenolic compounds in areca nut, green tea, walnut, etc. Preclinical studies have shown that GA possesses different pharmacological effects including anti-oxidant, antiapoptotic (Sohi et al., 2003). In a PF model, the rats were given GA orally at doses (50, 100, and 200 mg/kg/day) for 28 consecutive days started 7 days before the administration of single intratracheal instillation of BLM (Nikbakht et al., 2015). The results showed that oral administration of GA significantly reversed the increase of inflammatory or fibrotic changes, collagen content, levels of MDA, and pro-inflammatory cytokines such as TNF- α and IL-1 β , and the decrease of non-enzymatic (total thiol) and enzymatic (GPx) antioxidant contents in the rats' lung tissue induced by BLM. Thus, the supplement with GA as an adjuvant therapy in fibrotic lung disease may be a promising compound in reducing the side effects of BLM (Nikbakht et al., 2015). Therefore, further data *in vivo* and in clinical are indispensable to confirm its role in this area.

Salvianolic acids, the main active water-soluble extracts of *Salvia miltiorrhiza* Bunge (commonly known as 'Danshen'), have a remarkable curative effect on patients of silicosis combined with cor pulmonale (Wang and Zhao, 2016), the principle poly-phenolic acids of which include salvianolic acid A (SAA) and SAB. BLM (5 mg/kg; intratracheal injection)-treated rats exhibited increased alveolar wall thickness and collagen deposition in lung tissues, but these were greatly attenuated by daily tail-vein injection of SAA (2.5, 5, and 10 mg/kg) (Pan et al., 2014). In the *in vitro* work, SAA significantly inhibited the proliferation, adhesion and migration of a stable cell line of murine 3T6 embryonic FB, partly due to its strong induction of cell cycle arrest and apoptosis. Consistently, the decreased expression of the cell cycle-related proteins cyclin D1, cyclin E1, and cyclin B1, and increased expression of p53 and p21 were observed in SAA-treated cells. In addition, the anti-apoptotic Bcl-2 protein decreased in a dose-dependent manner, while cleaved caspase-3 protein increased upon SAA treatment (Pan et al., 2014). However, it lacks the evidence whether SAA might reverse the symptoms of the late stage of established *in vivo* PF model. A recent work has showed the antiplatelet efficiency of SAB in acute coronary syndrome patients undergoing treatment with clopidogrel plus aspirin (Liu et al., 2014). In another work, the treatment with only SAB did not affect the proliferation and differentiation of human MRC-5 embryonic lung FB (Zhang et al., 2014b). Interestingly, SAB (1 or 10 μ mol/l) significantly inhibited TGF- β 1-induced cell proliferation, Col-I expression, endogenous TGF- β 1 production, and α -SMA expression in lung FB. Moreover, the inhibitory effect of SAB on TGF- β 1-induced proliferation and differentiation in lung FB was more significant when treated with high-dose SAB (Zhang et al., 2014b). Nevertheless, further investigations are required to explore the anti-fibrotic role of SAB in animal models and patients with PF.

3.5. Alkaloids

Neferine is a bisbenzylisoquinoline alkaloid which has proved to inhibit platelet aggregation in patients with hyperlipidemias (Shi and Hu, 1998). Recent work showed that neferine treatment (20 mg/kg, oral, b.i.d) showed less inflammation and fibrosis, suppressed the increased content of Hyp, and levels of MDA, MPO, TNF- α , IL-6 and endothelin-1 (in lung tissue or in plasma), while reversed the decreased SOD activity that triggered by intratracheal BLM administration in mice (Zhao et al., 2010). Additionally, neferine blocked BLM-induced increase of NF- κ B in nuclear extracts and TGF- β 1 in total protein extracts of murine RAW264.7 macrophages. The beneficial effect of neferine might be associated with its activities of anti-inflammation, anti-oxidation and cytokine inhibition (Zhao et al., 2010). Besides, further study showed the effects of neferine (20 mg/kg, oral, b.i.d) after

the third amiodarone instillation on a mouse PF model which was developed through intratracheal instillation of amiodarone (6.25 mg/kg) on the 1st, 3rd and 5th day (Niu et al., 2013a). This work declared that neferine significantly restored the significant reductions in body weights, the increased levels of lung index and Hyp, the abnormal histological findings, the serum surfactant protein-D (SP-D) increase, the Th1/Th2 imbalance by decreasing IL-4 and increasing IFN- γ levels and the increase in the population of CD4⁺CD25⁺ Tregs associated with amiodarone instillation in mice (Niu et al., 2013a). These results at least indicated the beneficial effect of neferine on the patients treated with BLM or amiodarone by alleviating above undesirable outcomes.

Isoliensinine, a bisbenzylisoquinoline alkaloid extracted from the seed embryo of *Nelumbo nucifera* Gaertn., which served as "heat-clearing drugs", has been considered to prevent BLM-induced PF in mice (Xiao et al., 2005). Isoliensinine (10, 20, 40 mg/kg; oral, tid) was administered for 14 days after intratracheal treatment with a single dose of BLM while the control group was instead of intratracheal saline. Administration of isoliensinine not only remarkably suppressed the increased Hyp content in the lungs, abated the lung histological injury, but also reversed the up-regulated MDA level and enhanced the SOD activity in the lungs and serum induced by BLM in a concentration-dependent manner (Xiao et al., 2005). Moreover, isoliensinine also significantly inhibited the over-expression of TNF- α and TGF- β 1 induced by BLM. These results shed light on the inhibitory effect of isoliensinine on BLM-induced PF, but further evidence is necessary to investigate its role on PF *in vitro* (Xiao et al., 2005). Whereas, the related effects of this compound on patients with PF or other lung diseases need to be uncovered.

Corydalis *yanhusuo* and its active ingredients tetrahydropalmatine (THP) have curative effect on senile chronic bronchitis in patients (Chen, 2016) and irradiation-induced lung injuries in rats, respectively (Yu et al., 2016). It was reported that pretreated with THP decreased lung injury by inhibiting the lung cells apoptosis as evidenced by decreased levels of apoptotic mediators (cytochrome c and caspase-3), suppressed lung inflammation by decreasing BALF cells recruitment and inflammatory cytokines levels (TNF- α , IL-6, and TGF- β 1), reduced PF by lowering Hyp content and MDA level in comparison to those irradiated alone (Yu et al., 2016). Moreover, the THP combined with IR group, had comparatively integrity pulmonary alveoli structure, less infiltration of inflammatory cells and unapparent alveolar septa thickening. These data indicate the potential role of THP in attenuating lung injury and fibrosis. However, further studies on the role of Corydalis *yanhusuo* and THP in alleviating PF are necessary. Due to its involvement in possessing multiple biologic activities, THP may act the anti-fibrotic effects through other unknown mechanisms.

Oxymatrine (OM) is a bioactive alkaloid constituent derived from *Sophora flavescens* Ait. (kurorinone, Kushen in Chinese) that has been approved by the State Food and Drug Administration of China for treating hepatitis B (Wang et al., 2011b). Liu et al. (2012) demonstrated the anti-fibrotic therapeutic benefit treated with daily OM (10, 20 or 40 mg/kg) one day after endotracheally instilled with BLM for 21 days in mice. In this study, OM improved BLM-induced lung pathological changes, reduced MPO activity and MDA levels, inhibited the release of TNF- α and IL-6, decreased the expression of iNOS in lung tissues and thus prevented NO release in response to BLM challenge in a dose-dependent manner (Liu et al., 2012). In addition, OM decreased the expression of TGF- β 1, p-Smad2 and p-Smad3 in the lungs. It indicated that OM could attenuate BLM-induced PF in mice *via* the inhibition of pro-inflammatory cytokine expression and the TGF- β /Smad pathway. Besides, OM prevented NO over-production through reducing iNOS expression in mouse lungs (Liu et al., 2012). These results suggest that OM may be a promising candidate for the prevention of lung damage or interstitial PF. However, the precise mechanism whereby OM inhibits iNOS expression and the protective role of OM on the established PF model or PF patients, should be clarified.

3.6. Other single component from herbs

A recent study has confirmed that osthole (7-methoxy-8-isopentoxycoumarin), a natural coumarin, appears to confer a protective effect in PF. The PF mode rats were induced by instilled intratracheally BLM and then subsequently administered osthole (40 mg/kg; the first dose was after instilling BLM for 1 h) by gavage daily until four weeks (Hao and Liu, 2016). The authors found that osthole treatment attenuated BLM-induced PF changes and diffused lung inflammation, significantly decreased the body weight loss, lung index and the expression of the inflammatory mediators (IL-6, TNF- α , IL-1 β), ANG II and TGF- β 1, and reversed ACE-2 and ANG-(1–7) production in rat lungs (Hao and Liu, 2016). It indicates that osthole exerts beneficial effects on BLM-induced rat PF, which perhaps *via* modulating the ACE-2/ANG-(1–7) axis and inhibiting lung inflammation.

Gamboge is a dried yellow resin secreted by *Garcinia hanburyi* Hook.f. [Clusiaceae (Guttiferae)] in Southeast Asia, while gambogic acid (GBA) is the main active compound. It demonstrated that GBA prevented TGF- β 1 stimulated EMT with a decrease in vimentin and p-Smad3, and an increase in E-cadherin in A549 AEC, while suppressed endothelial-mesenchymal transition (EndoMT) with a decrease in vimentin and an increase in VE-cadherin in human pulmonary microvascular endothelial cells (HPMECs), respectively (Qu et al., 2016). Moreover, GBA treatment inhibited TGF- β 1 and CoCl₂ stimulated human lung fibroblasts (HLF)-1 proliferation with reduction of platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF)-2, and ameliorated BLM-induced PF with a lower rate of Vasohibin-2 (VASH-2; an endogenous and vascular endothelial growth factor (VEGF)-independent angiogenic factor)/VASH-1 (a unique endogenous angiogenesis inhibitor) at early stage of fibrosis, and reduction of the pathological score, collagen deposition, as well as the expression of α -SMA, PDGF and FGF-2 at fibrotic stage (Qu et al., 2016). Previously, a phase I human tolerability trial of GBA showed that its maximal tolerated dose and dose-limiting toxicity is involved with liver dysfunction and pain in cancer patients, and thus further work to investigate its anti-fibrotic effect in clinical should consider these key factors (Zhou and Wang, 2007b).

4. Volatile oil from herbs for the therapy of PF

4.1. Volatile extract of *Houttuynia cordata* Thunb

Houttuynia cordata Thunb. (HC) had been previously evaluated owning the activities to resist severe acute respiratory syndrome (SARS) in patients, due to its role in decreasing patients mortality rate and improving arthralgia, myalgia as well as arterial oxyhemoglobin saturation (Li et al., 2006). HC volatile extract was applied to a LPS-induced rapid pulmonary fibrosis (RPF) rat model and analyzed its effect on ALI and RPF (Du et al., 2012) (Table 2). The active ingredients of the HC vapor extract included 4-terpineol, α -terpineol, L-bornyl acetate and methyl-n-nonyl ketone by gas chromatograph-mass spectrometer (GC-MS) (Du et al., 2012). *In vitro*, HC vapor extract could inhibit the viability of RAW264.7 and NIH/3T3 cells, and dose-dependently decreased the expression of TGF- β 1 and enhanced the expression of IFN- γ in NIH/3T3 embryonic FB (Du et al., 2012). In addition, α -terpineol enhanced IFN- γ expression in NIH/3T3 embryonic FB and inhibited the growth of RAW 264.7 macrophages, while L-bornyl acetate presented the opposite effects, but both of them inhibited the growth of NIH/3T3 in a dose-dependent manner. In LPS-induced rat RPF, HC vapor extract treatment evidently up-regulated the ratio of lymphocytes and mononuclear phagocytes at the 7th day, reduced the expression of TGF- β 1 and Smad2/3, the content of lung Hyp (16.5 mg/kg) and serum LDH, and increased the expression of IFN- γ and Smad7 (Du et al., 2012). Current investigation shows that the pharmacologically active ingredients of HC vapor extract might be α -terpineol and L-bornyl acetate, which reduced ALI

Table 2
The studies of volatile oil from herbs for the therapy of PF.

Volatile oil	Herbs	Detection	Objects (model inducers, doses)		Effects	Ref.
			<i>In vitro</i>	<i>In vivo</i>		
HC	<i>Houttuynia cordata</i> Thunb.	GC-MS	RAW264.7 macrophages, NIH/3T3 embryonic FB (LPS, 100 ng/ml)	Wistar rats (LPS, 3 mg/kg)	SARS patients	Mortality rate \downarrow , life quality \uparrow TGF- β 1/Smads signal \downarrow , IFN- γ \uparrow Li et al. (2006) Du et al. (2012)
α -terpineol						
L-bornyl acetate						
NS volatile oil	<i>Nigella sativa</i> L.			Wistar albino rats (hydrochloric acid, 2 ml/kg)		IFN- γ \uparrow , NIH/3T3 FB \downarrow IFN- γ \downarrow , NIH/3T3 FB \downarrow iNOS \downarrow , SP-D \uparrow Kanter (2009)
Alicin	<i>Allium sativum</i> L.			SD rats (CP, 150 mg/kg)		LDH \downarrow , TNF- α \downarrow , reduced GSH \uparrow Ashry et al. (2013)

CP: cyclophosphamide; FB: fibroblasts; GC-MS: gas chromatograph-mass spectrometer; GSH: glutathione; HC: *Houttuynia cordata*; IFN: interferon; iNOS: inducible nitric oxide synthase; PF: pulmonary fibrosis; LDH: lactate dehydrogenase; LPS: lipopolysaccharide; NS: *Nigella sativa*; SARS: severe acute respiratory syndrome; SP-D: surfactant protein-D; TGF- β 1: transforming growth factor- β 1; TNF- α : tumor necrosis factor- α

and RPF, while IFN- γ and the TGF- β 1/Smad pathway might be the pharmacological targets of HC. Considering a fact that the final development of SARS symptom is similar to that of PF, digging the role of HC or its vapor monomers in PF would be more attractive.

4.2. Volatile oil of *Nigella sativa* L

The black seeds of *Nigella sativa* L. (NS), contain > 30% of fixed oil and 0.4–0.45% wt/wt of volatile oil (thymoquinone, p-cymene, a-pi-ene, etc.), and have beneficial effects on asthma and dyspnea, digestive and gynecology disorders (Gholamnezhad et al., 2015; Kanter, 2009; Keyhanmadesh et al., 2014). In the study, the saline, Pulmocare (a specialized nutritional supplement given to pulmonary patients) and hydrochloric acid were injected into the rats' lungs in a volume of 2 ml/kg to develop experimental lung injury, and then the rats received daily oral doses of NS volatile oil (400 mg/kg body weight) by means of intragastric intubation for 7 days starting immediately after the lung aspiration of these materials (Kanter, 2009) (Table 2). The results showed that NS volatile oil treatment inhibited the inflammatory lung responses, evidently reduced the peribronchial inflammatory cell infiltration, alveolar septal infiltration, alveolar edema, alveolar exudate, alveolar macrophages, interstitial fibrosis, granuloma and necrosis formation, with a significant reduction in the activity of iNOS and a rise in SP-D, (a mediator of innate host defense and inflammation) in different lung aspiration models (Kanter, 2009). Later, Boskabady and colleagues completed a study in asthmatic patients, which showed that treatment with the boiled extract of NS could increase the suffers' lung function (Boskabady et al., 2010). These results indicate that NS volatile oil might be beneficial in lung interstitial fibrosis with potential therapeutic properties in a clinical setting.

4.3. Allicin

Allicin (diallylthiosulphinate), one of the active compounds of freshly crushed garlic (*Allium sativum* L.), possesses a variety of biological activities such as antimicrobial, anti-inflammatory, anti-thrombotic, anti-atherosclerotic, serum lipid lowering and anticancer activities (Shadkchan et al., 2004). The injury of normal tissues is the major limitation of using cyclophosphamide (CP), a cytotoxic alkylating agent that has been widely used in the treatment of various neoplastic diseases and autoimmune disorders. Meanwhile, lack of detoxifying enzymes, aldehyde oxidase and aldehyde dehydrogenase in the lungs is a cause of selective CP toxicity to lung tissue. Ashry and colleagues carried out a study to assess whether allicin (50 mg/kg/d, p.o.) can ameliorate CP (150 mg/kg, i.p.)-induced early lung injury in male SD rats (Ashry et al., 2013) (Table 2). It showed that a single intraperitoneal pretreatment of rats daily with oral allicin seven days prior to and seven days after CP injection effectively blunted CP-induced histopathological changes, significantly reduced the increase of lung index and serum levels of total protein, LDH and TNF- α , and reversed the decrease of total reduced GSH level with increased survival rate of the rats (Ashry et al., 2013). The results indicate that allicin may partially protects healthy lung against CP injury. Recent work provided evidence that allicin could improve the burning sensation, mouth opening, and oral health-related quality of life in these stage II oral submucous fibrosis patients (Jiang et al., 2015b). It further encourages the special work of allicin on the fibrotic lung disease.

5. Multiple components from single herbs for the therapy of PF

5.1. Safflor yellow

SY (Safflor yellow) is the effective part of the aqueous extract of *Carthamus tinctorius* L.. The authors investigated the effects of SY (intraperitoneal, 25, 50 mg/kg/d) on the rats of PF induced by BLM

(consecutively for four weeks) and on differentiation of HELFs into MFb stimulated by TGF- β 1 (Wang et al., 2011a). The data showed that SY alleviated the loss of body weight, the increase of lung Hyp content, α -SMA positive cells, and TGF- β 1 expression, as well as the pathologic changes of PF caused by BLM instillation. Furthermore, suitable concentrations of SY inhibited α -SMA expression during TGF- β 1-stimulated differentiation of lung FB into MFb (Wang et al., 2011a). In a study of 70 PF patients that treated with methylprednisolone (oral, 0.4 mg/kg daily) or a combined drugs (SY sodium chloride injection (100 ml daily, containing 80 mg SY) and methylprednisolone (oral, 0.4 mg/kg daily)), the authors observed that the scores of cough, dyspnea, cyanosis, rales and total score of the combined drugs treatment group were significantly lower than those of methylprednisolone group (Sun et al., 2016). Moreover, the FEV1/(forced vital capacity, FVC) was significantly higher than those in the methylprednisolone group, while the serum levels of hyaluronic acid, laminin, procollagen III, Col-III and blood urea nitrogen were significantly lower than those in the single drug treatment group (Sun et al., 2016). It may provide direct evidence of SY application in PF patients.

5.2. Triterpene acids of *Eriobotrya japonica* (Thunb.) Lindl

It was found that triterpene acids of *Eriobotrya japonica* (Thunb.) Lindl. leaf (TAL), which were analyzed by HPLC containing ursolic acid, oleanolic acid, etc., could reduce BLM-induced alveolar structure destruction and collagen expression in rats (Yang et al., 2012a). Additionally, TAL decreased the expression of TNF- α and TGF- β 1 in the culture supernatant of AMs that obtained from the BALF of BLM-induced rats. Recent data showed that *Eriobotrya japonica* (Thunb.) Lindl. leaf drink was demonstrated to obviously alleviate the gastrointestinal side effects of chemotherapy and improved the living quality of middle-late stage lung cancer patients (Lin, 2015). However, no evidence shows whether loquat, TAL or the herb derivatives have improved effects on PF suffers.

5.3. Boswellic acids

Boswellic acids (BA) are found in the gum resin of *Boswellia serrata* Roxb. ex Colebr. in parts of China and India. In the treatment of gonarthrosis, BA was shown to significantly reduce the patients' need for anti-inflammatory drugs (Notarnicola et al., 2011). While in the study of PF, BA (1 g/kg) reduced the number of infiltrating cells, ameliorated the destruction of lung architecture and attenuated BLM-induced PF in rats. Additionally, BA-treated rats had reduced number of macrophages, neutrophils in BALF, significantly lowered content of LDH and LPO in serum, and reduced levels of Hyp, TGF- β 1, TNF- α , and 5-lipoxygenase (5-LOX) in lung tissue (Ali and Mansour, 2011). In contrast, the reduction of the activities of antioxidant events (SOD, GSH, CAT) in the blood and lung homogenate of the fibrotic rat were evidently reversed with BA treatment. This work suggests the prevention of BA on lung injury and fibrosis in rats, but it is unclear of its role in PF patients.

5.4. *Rhodiola rosea* L

In a performed study in 40 cases of PF patients, Dazhu Hongjingtian (*Rhodiola rosea* L.) injection (Tonghua Yusheng Medicine Co., Ltd., China, 10 ml daily) in combination with conventional therapy of oral prednisone could significantly increase the patients' partial pressure of oxygen, maximum amount of pulmonary ventilation, pulmonary diffusion and total efficacy, but obviously decrease the symptom scores, which were better than those in the only conventional therapy of oral prednisone (Yang, 2014). However, the patient sample is not enough to clarify its clinical benefits. The studies to investigate its possible side effects on the *in vivo* models should be considered first if further clinical trials were conducted.

5.5. *Hirsutella sinensis mycelium*

Hirsutella sinensis mycelium (HSM), the anamorph of *Cordyceps sinensis*, a parasitic fungus that infects larvae of ghost moths, is a TCM that has emerged as an attractive substitute for the preparation of health supplements (Paterson, 2008). In a performed clinical study, *Cordyceps sinensis* extract-bailing capsule dosage (60 mg/(kg day)) in combination with methylprednisolone more obviously improved the total clinical cure rate, the arterial blood gas analysis and percentage of predicted FVC than patients receiving only methylprednisolone in PF patients (Li et al., 2015c). Notably, a recent study provided the experimental evidence that HSM ethanol extract attenuates lung inflammation and fibrosis (Huang et al., 2015). *In vitro*, the pretreatment with HSM inhibited TGF- β 1-induced FN, α -SMA, p-Smad2/3

and p-Akt expression, and restored SOD expression in MRC-5 lung FB, while inhibited ROS production in mouse MLE12 lung epithelial cells (Huang et al., 2015). Furthermore, HSM improved BLM-induced histopathological changes with decreased alveolar wall thickness, inflammatory cell infiltration, vascular congestion, and alveolar space collapse, accompanied by reduced collagen deposition and Ashcroft score, reversed total cell and leukocyte accumulation in BALF, attenuated the expression of IL-1 β , IL-18, TGF- β 1, Col-3 α 1, α -SMA, NOD-like receptor (NLRP)-3, P2 \times 7R (a purinergic receptor that activates NLRP3 inflammasome), and caspase-1 activation in the lungs of BLM-treated mice (Huang et al., 2015). These data suggest that *Cordyceps sinensis* and HSM may be promising materials in protecting against PF.

Table 3

The herbal sources of TCM formulations and their extracts in the PF studies.

Agents	Herbal sources (ratio)	Ref.
Renshen pingfei decoction	<i>Panax ginseng</i> C.A.Mey., <i>Asparagus cochinchinensis</i> (Lour.) Merr., <i>Morus alba</i> L., <i>Lycium chinense</i> Mill., <i>Glycyrrhiza uralensis</i> Fisch., <i>Anemarrhena asphodeloides</i> Bunge, <i>Citrus reticulata</i> Blanco (1:1:1:1:1:1)	Chen et al. (2016b)
Hu-qi-yin	<i>Polygonum cuspidatum</i> Sieb. et Zucc., <i>Astragalus membranaceus</i> (Fisch.) Beg. var. <i>mongholicus</i> (Beg.) Hsiao, <i>Salvia miltiorrhiza</i> Bge., <i>Ligusticum chuanxiong</i> Hort., <i>Angelica sinensis</i> (Oliv.) Diels, <i>Citrus reticulata</i> Blanco, <i>Glycyrrhiza uralensis</i> Fisch. (the per centum is 13%: 26%: 26%: 13%: 9%: 9%: 4%)	Zhou et al. (2007a)
Runfei decoction	<i>Seeds of Prunus davidiana</i> (Carr.) Franch., <i>Glycyrrhiza glabra</i> L., <i>Platycodon grandiflorus</i> (Jacq.) A.DC., <i>Ephedra equisetina</i> Bunge, <i>Prunus armeniaca</i> L., <i>Lycium chinense</i> Mill., <i>Morus alba</i> L., <i>Inula japonica</i> Thunb., <i>Lilium brownii</i> F.E.Br. ex Miellez, <i>Adenophora stricta</i> Miq., <i>Paeonia lactiflora</i> Pall., CaSO ₄ ·2H ₂ O (10 g: 10 g: 10 g: 10 g: 10 g: 10 g: 12 g: 15 g: 20 g: 30 g: 30 g: 30 g)	Mei (2014)
Shenlong decoction	<i>Astragalus mongholicus</i> Bunge, <i>Adenophora stricta</i> Miq., <i>Rehmannia glutinosa</i> (Gaertn.) DC., <i>Pheretima aspergillum</i> (E. Perrier), <i>Angelica sinensis</i> (Oliv.) Diels, <i>Ligusticum striatum</i> DC., <i>Glycyrrhiza glabra</i> L. (25 g: 30 g: 10 g: 10 g: 15 g: 15 g: 10 g)	Lu et al. (2010)
Qingre Huoxue Sanjie formula	<i>Scutellaria baicalensis</i> Georgi, <i>Forsythia suspensa</i> (Thunb.) Vahl, <i>Paeonia suffruticosa</i> Andr., <i>Paeonia veitchii</i> Lynch, <i>Iphigenia indica</i> Kunth, <i>Prunella vulgaris</i> L., etc. (12 g: 12 g: 10 g: 10 g: 15 g: 15 g)	Tian et al. (2014)
DSQRL decoction	<i>Panax ginseng</i> C.A.Mey., <i>Astragalus mongholicus</i> Bunge, <i>Ophiopogon japonicus</i> (Thunb.) Ker Gawl., <i>Angelica sinensis</i> (Oliv.) Diels, <i>Salvia miltiorrhiza</i> Bunge, <i>Ligusticum striatum</i> DC. (15 g: 30 g: 15 g: 10 g: 15 g: 15 g)	Zhang et al. (2007, 2008)
Huqi Huoxue decoction	<i>Reynoutria japonica</i> Houtt., <i>Astragalus mongholicus</i> Bunge, <i>Salvia miltiorrhiza</i> Bunge, <i>Ligusticum striatum</i> DC., <i>Angelica sinensis</i> (Oliv.) Diels, <i>Citrus reticulata</i> Blanco, <i>Glycyrrhiza uralensis</i> Fisch., etc. (unprovided ratio)	Zhang et al. (2014a)
Huaxian formula	<i>Bupleurum chinense</i> DC., <i>Scutellaria baicalensis</i> Georgi, <i>Codonopsis pilosula</i> (Franch.) Nannf., <i>Pinellia ternata</i> (Thunb.) Makino, <i>Trichosanthes kirilowii</i> Maxim., <i>Cinnamomum cassia</i> (L.) J.Presl, <i>Schisandra chinensis</i> (Turcz.) Baill., <i>Zingiber officinale</i> Roscoe, <i>Trichosanthes kirilowii</i> Maxim., <i>Cyperus rotundus</i> L., <i>Glycyrrhiza glabra</i> L., <i>Fritillaria thunbergii</i> Miq., <i>Ophiopogon japonicus</i> (Thunb.) Ker Gawl. (24 g: 9 g: 15 g: 12 g: 12 g: 12 g: 15 g: 6 g: 15 g: 12 g: 6 g: 12 g: 15 g)	Cheng (2015)
mKG formula	<i>Angelica sinensis</i> (Oliv.) Diels., <i>Sophora flavescens</i> Aiton, <i>Glycyrrhiza uralensis</i> Fisch. (160 g: 60 g: 60 g)	Gao et al. (2016)
TJ-19 formula	<i>Pinellia ternata</i> (Thunb.) Makino, <i>Glycyrrhiza glabra</i> L., <i>Cinnamomum verum</i> J.Presl, <i>Schisandra chinensis</i> (Turcz.) Baill., <i>Erigeron breviscapus</i> (Vaniot) Hand.-Mazz., <i>Paeonia lactiflora</i> Pall., <i>Ephedra sinica</i> Stapf, <i>Zingiber officinale</i> Roscoe (9 g of each ingredient)	Yang et al. (2010)
TQABDA method	<i>Astragalus mongholicus</i> Bunge, <i>Curcuma phaeocaulis</i> Val., <i>Salvia miltiorrhiza</i> Bge., <i>Angelica sinensis</i> (Oliv.) Diels, <i>Fritillaria cirrhosa</i> D.Don, <i>Scutellaria baicalensis</i> Georgi, <i>Curcuma aromatica</i> Salisb., etc. (20 g: 10 g: 20 g: 15 g: 10 g: 10 g: 10 g)	Sun et al. (2008)
Bufe Huoxue decoction	<i>Astragalus mongholicus</i> Bunge, <i>Codonopsis pilosula</i> (Franch.) Nannf., <i>Carthamus tinctorius</i> L., <i>Fritillaria thunbergii</i> Miq., <i>Salvia miltiorrhiza</i> Bge., <i>Ligusticum chuanxiong</i> , <i>Angelica sinensis</i> (Oliv.) Diels, <i>Lilium brownii</i> F.E.Br. ex Miellez, <i>Ginkgo biloba</i> L., <i>Citrus aurantium</i> L., <i>Perilla frutescens</i> (L.) Britt., <i>Allium macrostemon</i> Bunge., etc. (30 g: 20 g: 10 g: 15 g: 30 g: 10 g: 10 g: 10 g: 10 g: 10 g: 10 g: 10 g)	Wu and Zhang (2010)
Qingjin decoction	<i>Astragalus mongholicus</i> Bunge, <i>Pseudostellaria heterophylla</i> (Miq.)Pax., <i>Cornus officinalis</i> Siebold & Zucc., <i>Epimedium sagittatum</i> (Siebold & Zucc.) Maxim., <i>Pheretima aspergillum</i> (E. Perrier), <i>Prunus davidiana</i> (Carr.)Franch., <i>Paeonia lactiflora</i> Pall., <i>Ligusticum striatum</i> DC., <i>Buthus martensii</i> Karsch, <i>Hirudo nipponica</i> Whitman, <i>Smilacis Glabrae</i> , etc. (30 g: 30 g: 15 g: 15 g: 15 g: 15 g: 30 g: 15 g: 15 g: 8 g: 15 g)	Wong and Ma (2011)
Yangyin Yiqi formula	<i>Codonopsis pilosula</i> (Franch.) Nannf., <i>Ophiopogon japonicus</i> (Linn. f.) Ker-Gawl., <i>Lilium brownii</i> F.E.Br. ex Miellez, <i>Rehmannia glutinosa</i> (Gaertn.) DC., <i>Pinellia ternata</i> (Thunb.) Makino, <i>Glehnia littoralis</i> F.Schmidt ex Miq., <i>Fritillaria przewalskii</i> Maxim. ex Batalin., <i>Polygonatum odoratum</i> (Mill.) Druce, <i>Atractylodes macrocephala</i> Koidz., <i>Astragalus mongholicus</i> Bunge, <i>Platycodon grandiflorus</i> (Jacq.) A.DC., <i>Aster tataricus</i> L.f., <i>Bambusa tuldoidea</i> Munro, <i>Schisandra chinensis</i> (Turcz.) Baill. (20 g: 20 g: 20 g: 20 g: 10 g: 10 g: 10 g: 10 g: 15 g: 15 g: 15 g: 15 g: 15 g)	Wang and Ren (2014a)
Jade Screen Powder	<i>Astragalus mongholicus</i> Bunge, <i>Saposhnikovia divaricata</i> (Turcz.) Schischk., <i>Stephania tetrandra</i> S.Moore, <i>Platycodon grandiflorus</i> (Jacq.) A.DC, <i>Lonicera japonica</i> Thunb., <i>Mentha spicata</i> L., <i>Schisandra chinensis</i> (Turcz.) Baill., etc. (40 g: 10 g: 15 g: 15 g: 12 g: 12 g: 15 g)	Yang et al. (2012b)
YPF-G	<i>Astragalus mongholicus</i> Bunge, <i>Atractylodes macrocephala</i> Koidz., <i>Saposhnikovia divaricata</i> (Turcz.) Schischk. (the ratio is 3:1:1)	Li et al. (2015b) and Cui et al. (2015)
YPF-P		Xu et al. (2014)
DBTG	<i>Astragalus mongholicus</i> Bunge, <i>Angelica sinensis</i> (Oliv.) Diels (the ratio is 5:1)	Gao et al. (2011, 2012) and Zhao et al. (2015b)

DBTG, total glucosides of Danggui-Buxue-Tang; DSQRL, decoction for Strengthening Qi and Replenishing Lung; mKG, Modified Kushen Gancao; TJ-19, Sho-seiryu-to; TQABDA, Tonifying Qi, Activating Blood and Dispersing Accumulation; YPF-G, total glycoside of Yupingfeng; YPF-P, total polysaccharides of Yupingfeng

Table 4
The benefits of TCM formulations and their extracts for the therapy of PF.

Agents	Detection	Sample (inducer)		Actions	Ref.
		<i>In vivo</i>	Patients		
Renshen pingfei decoction	UPLC-QTOF-MS	SD rats (BLM)	–	TGF-β1/Smads signal ↓, NF-κB ↓, oxidative stress ↓	Chen et al. (2016b)
Hu-qi-yin	–	SD rats (BLM)	–	Hyp ↓, TGF-β1 ↓	Zhou et al. (2007a)
Runfei decoction	–	–	Lung cancer patients (Thoracic radiotherapy)	Radioactive PF incidence ↓, TGF-β ↓, IL-6 ↓	Mei (2014)
Shenlong decoction	–	Wistar rats (BLM)	–	MMP-2/TIMP-1 imbalance ↓	Lu et al. (2010)
Qingre Huoxue Sanjie formula	–	–	Lung cancer, esophageal cancer or thymoma patients (Chest radiotherapy)	Radioactive PF incidence ↓, life quality ↑, TGF-β1 ↓, IL-6 ↓, TNF-α ↓	Tian et al. (2014)
DSQRL decoction	–	SD rats (GC14)	–	TGF-β1 ↓	Zhang et al. (2007, 2008)
Huqi Huoxue decoction	–	–	PF patients	Curative effect ↑, adverse reaction ↓, treatment cost ↓	Zhang et al. (2014a)
Huaxian formula	–	–	Radiation-induced PF patients	Movement limitation ↓, disease impaction ↓, pulmonary function ↑	Cheng (2015)
mKG formula	UPLC-MS/MS and GC-MS	BALB/c mice (BLM)	–	Collagen ↓, inflammation ↓, TGF-β1 ↓, α-SMA ↓	Gao et al. (2016)
TJ-19 formula	Three-Dimensional HPLC	SD rats (BLM)	–	Hyp ↓, MDA ↓	Yang et al. (2010)
TQABDA method	–	–	PF patients	Alveoli ↓, TGF-β1 ↓	Sun et al. (2008)
Buifei Huoxue decoction	–	–	PF patients	Effective rate ↑, PaO ₂ ↑, total lung capacity ↑, CO diffusion capacity ↑, symptomatic score ↓, PaCO ₂ ↓	Wu and Zhang (2010)
Qingjin decoction	–	–	PF patients	Lung function ↑, PaO ₂ ↑, hypoxia ↓, PaCO ₂ ↓	Wong and Ma (2011)
Yangyin Yiqi formula	–	–	PF patients	Total effective rate ↑, FEV1 ↑, FEV1/FVC(%) ↑, TGF-β1 ↓	Wang and Ren (2014a)
Jade Screen Powder	–	–	PF patients	Curative effect ↑, Karnofsky scores ↑, FEV1 ↑, FVC ↑, FEV1/FVC ↑, TGF-β1 ↓	Yang et al. (2012b)
YPF-G	HPLC-ELSD	SD rats (BLM)	–	ECM ↓, TGF-β1 ↓, HMGB1 ↓, EMT ↓	Li et al. (2015b) and Cui et al. (2015)
YPF-P	HPLC-GPC	SD rats (BLM)	–	ECM ↓, TGF-β1 ↓	Xu et al. (2014)
Total glucosides of Danggui-Buxue-Tang	HPLC-ELSD	SD rats (BLM)	–	ECM ↓, TNF-α ↓, MMP-9/TIMP-1 imbalance ↓, TGF-β1 ↓, α-SMA ↓, oxidative stress ↓	Gao et al. (2011, 2012) and Zhao et al. (2015b)

BLM: bleomycin; GC14: carbon tetrachloride; DSQRL: Decoction for Strengthening Qi and Replenishing Lung; ECM: extracellular matrix; EMT: epithelial-mesenchymal transition; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; GC, gas chromatography; HPLC, high-performance liquid chromatography; HMGBl: high-mobility group box 1; HPLC, high-performance liquid chromatography; Hyp: hydroxyproline; IL: interleukin; MDA: malondialdehyde; mKG: Modified Kushen Gancao Formula; MMP: matrix metalloproteinase; MS, mass spectrometry; NF-κB: nuclear factor kappa B; PF: pulmonary fibrosis; QTOF, quadrupole time-of-flight; TGF-β1: transforming growth factor-β1; TIMP: tissue inhibitor of metalloproteinase; TJ-19, Sho-seiryu-to; TNF-α: tumor necrosis factor-α; TQABDA, Tonifying Qi, Activating Blood and Dispersing Accumulation; UPLC, ultra-performance liquid chromatography; YPF-G, total glycoside of Yupingfeng; YPF-P, total polysaccharides of Yupingfeng; α-SMA: α-smooth muscle actin

6. TCM formulations and their extracts for the therapy of PF

Due to numerous clinical practice, it is well recognized that TCM formulations could be more effective than an isolated single constituent for disease management. The past years have witnessed a number of studies investigating the benefits of the TCM formulations and their active agents for the treatment of PF (Tables 3 and 4). These formulas detail can be obtained from Table 3, whereas the composition of some formulas was not fully showed because the TCM prescription may add few other herbs based on the special patients or not, especially in some work in Chinese.

Chen et al. (2016b) detected 43 peak signals of the chemical components of Renshen pingfei decoction (RPFS) including mangiferin, caffeic acid, liquiritin, naringin, notoginsenoside R1, ginsenoside Rg1, etc. by UPLC-QTOF-MS analyses and evaluated the protective role of RPFS (6.5 g/kg daily) in a rat model of PF induced with BLM (5 mg/kg). RPFS exerted significant effects on PF model rats in improving lung function and decreasing Hyp content of lung tissue, reducing the levels of TGF- β 1 and NF- κ B in BALF, SOD and MDA levels in serum, as well as down-regulating TGF- β 1 and Smad3 mRNA and protein expression of lung tissue compared with model group (only BLM injection) (Chen et al., 2016b). It suggests that RPFS has protective role on experimental PF, which might mediated by down-regulating TGF- β 1/Smad3 signaling pathway. However, the role of the chemical components identified in RPFS is worthy of further study in PF treatment. Zhou and partners found that oral treatment with Hu-qi-yin (a prescription formulation) improved the body weight loss of rats compared with BLM-treated control group, and significantly reduced the over-expression of TGF- β 1 protein and mRNA, inhibited the alveolitis and PF as reflected by the decrease of the Hyp levels of serum and lung, and amelioration of alveolitis and PF scores 28 days after BLM administration (Zhou et al., 2007a). This work confirms that Hu-qi-yin administration by oral route possess protective and anti-fibrotic effects on BLM-induced PF in rats. Further studies are needed for clarifying the possible mechanisms of the protective and therapeutic effects of Hu-qi-yin as well as its active components.

Runfei decoction is composed of twelve kinds of herbs (Table 3). A clinical work showed that Runfei decoction (200 ml daily to the end of radiotherapy) could significantly reduce the incidence of radioactive pneumonia and PF, decrease the serum levels of TGF- β and IL-6 in patients with lung cancer (Mei, 2014) (Table 4). It was observed that BLM (4 mg/kg)-treated rats with the treatment of Shenlong decoction (0.6, 1.2, 2.4 g/ml crude drug) decreased the mRNA levels of MMP-2 and TIMP-1, especially the former, and this action continued to the 28th day with Shenlong decoction (1.2 g/ml crude drug) decreasing most obviously (Lu et al., 2010). Thus, Shenlong decoction may slow the progression of PF by maintaining the dynamic balance of MMP-2/TIMP-1 and reversing ECM deposition (Lu et al., 2010). However, the role of Shenlong decoction on the pathological changes in lung tissue of murine PF is unclear. Besides, the main ingredients of Shenlong decoction need to be identified and are worthy of further study in PF treatment. Qingre Huoxue Sanjie formula (200 ml daily to the end of radiotherapy) has also been demonstrated safe and effective in alleviating the incidence of radioactive pneumonia and PF, relieving pathological symptoms, improving patient quality of life, decreasing the serum levels of IL-6, TNF- α and TGF- β 1 in patients with lung cancer, esophageal cancer or thymoma but their chest radiotherapy must be identified (Tian et al., 2014).

As TCM considers PF as a condition of *Lung* weakness due to lack of *Qi* that is the vigor for the respiration and the life as a whole, the authors used a new decoction for Strengthening *Qi* and Replenishing *Lung* (DSQRL) to treat experimental PF induced by carbon tetrachloride (CCl₄) (1 ml/kg intra-peritoneally) in comparison with glucocorticoid treatment (Zhang et al., 2007). In the studies, four injections of CCl₄ were carried out on the 1st, 5th, 9th and 14th days of the experiment; on day 17, the corresponding dose of DSQRL and

prednisone acetate were given to the rats *via* a gastric feeding tube twice a day for another 30 days (Zhang et al., 2007) and 60 days (Zhang et al., 2008), respectively (Table 4). It showed that DSQRL (9 g/kg raw herbs daily) with or without prednisone significantly reduced CCl₄-induced increase of Hyp content in the lungs, decrease of cell counts in BALF, whereas prednisone alone did not; meanwhile, the growth rate and general conditions of the rats treated with DSQRL were better than the prednisone group (Zhang et al., 2007). Besides, DSQRL treatment (7.7 g/kg raw herbs daily) improved CCl₄-induced abnormality of the lung surface morphology, had a significant alleviation in PF as illustrated by less inflammatory changes, cellular infiltration and collagen distribution, showed a significant reduction in TGF- β 1 level (Zhang et al., 2008). These evidence show the potential merit of DSQRL holistic approach to treat PF. As CCl₄ is toxic to experimental animals in particular to the liver rather than as a specific treatment for PF, it warrants to test the treatments of DSQRL on other PF models induced by other methods such as BLM or radiation. In addition, DSQRL is worth pursuing investigation further, in particular to find out the active ingredients and isolate active compounds by modern methods. Other data have shown that the lung fibrosis of mice appears between 14 and 28 days after a single-dose BLM application, and within 6 weeks, the lung repairs itself and minimal to no evidence of fibrosis remains (Degryse et al., 2010), if so, the work design of observing the role of 60 days treatment with DSQRL on PF may have room for improvement (Zhang et al., 2008).

Huqi Huoxue decoction has recently been proven evidently effective in treating PF patients (Zhang et al., 2014a). The data showed that Huqi Huoxue decoction treatment has higher clinical curative effect, less adverse reaction and treatment cost than those in prednisone group (Zhang et al., 2014a). However, the ratio of the compound was not provided and the dosage is unclear in the article. Huaxian formula contains thirteen herbs (Table 3), which combined Western medicine could more improve the quality of life in patients with radiation-induced PF by reducing the respiratory symptoms, movement limitation, disease impaction and increasing the pulmonary function than the conventional Western medicine group (Cheng, 2015) (Table 4). The optimized three-herb TCM formula, Modified Kushen Gancao (mKG) Formula, which is derived from the famous formula Kushen Gancao Tang, consists of three herbs (Table 3). A recent study provided evidence that mKG formula significantly alleviated the collagen deposition (Masson staining) and alveolitis (HE staining), reduced the levels of IL-6, IL-17, TGF- β 1 and Hyp, and lowered the expression of Col-I, Col-III and α -SMA in lung tissue of mice compared with BLM treatment (Gao et al., 2016). This study not only demonstrate the anti-inflammatory properties of mKG, but also show some effects of regulating the ECM deposition and inhibiting the PF progression, and it may become an important method for preventing and treating PF.

The ethical Kampo formulation Sho-seiryu-to (TJ-19), a traditional medicine used throughout south-east Asia, is a mixture of eight herbal components (Table 3). Yang and partners identified the constituents of TJ-19 including liquiritin and glycyrrhizin (originating from Glycyrrhiza Root), paeoniflorin and albiflorin (Paeony Root), schizandrin (Schisandra Fruit), cinnamic aldehyde and cinnamic acid (Cinnamon Bark) and 6-gingerol (Ginger Rhizome) by three-dimensional HPLC analysis (Yang et al., 2010). In the study, TJ-19 was administered orally twice a day at a dose of 1.5 g/kg after intratracheal instillation of a single dose of BLM (5 mg/kg) in rats. TJ-19 treatment could prevent BLM-induced fibrotic changes in the lung histology, attenuate the loss in body weight, and increase in lung index and concentration of Hyp and MDA in the lungs induced by BLM (Yang et al., 2010). Above effects were observed when TJ-19 administration was started 1 week before and simultaneously with the instillation of BLM. It suggests that TJ-19 has prophylactic potential against BLM-induced PF, and may therefore be a promising drug candidate and medicinal resource for preventing PF (Table 4). Future work to examine the yield of the anti-oxidative components in TJ-19 and the

curative as well as prophylactic effects of each constituent on PF are urgently needed.

Sun and partners observed that Tonifying Qi, Activating Blood and Dispersing Accumulation (TQABDA) method (one dose daily) combined with conventional glucocorticoids strategy not only more improve the symptoms but also inhibit lung alveoli and TGF-β1 level in identified PF patients than those treated with glucocorticoids only, but the included patients were not so clearly identified (Sun et al., 2008) (Table 4). It was also showed that oral Bufe Huoxue decoction (150 ml once, two times daily) in combination with oral prednisone had higher total effective rate and PaO₂, lower symptomatic score and PaCO₂, and more improved lung function (increased total lung capacity, vital capacity and carbon monoxide diffusion capacity), also no abnormal changes of blood, urine, and liver and kidney function were observed (Wu and Zhang, 2010). Similarly, Qingjin decoction (one dose daily) combined with conventional prednisone also more obviously improved the lung function, hypoxia, arterial blood gas related indicators in PF patients than those treated with prednisone only (Wong and Ma, 2011). Yangyin Yiqi formula, contains 14 kinds of herbs, was recently demonstrated to effectively improve PF in patients with higher total effective rate (X-ray chest radiograph), FEV1 and FEV1/FVC(%), less serum TGF-β1 level, and shortened recovery time of night sweats, body emaciated, skin dryness, fatigue, loss of appetite and other symptoms after two weeks basic medication than those with oral prednisone treatment. Thus, it combination with glucocorticoids may reduce the dose of later and then alleviate the adverse effects to patients, but the applied dosage was not provided in the work (Wang and Ren, 2014a). Jade Screen Powder (100 ml once, two times daily) associated with prednisone more significantly improved the overall efficacy, curative effect (chest radiograph analysis), the quality of life (increased Karnofsky scores), lung function (increased FEV1, FVC, FEV1/FVC), and less serum TGF-β1 level in PF patients than the prednisone only strategy (Yang et al., 2012b). Though many clinical work showed that several formulas attenuated PF in patients, they contained so small sample sizes that further identification of its universal application may be more convince and necessary in different areas and hospitals.

Yupingfeng composes of three herbs in a dry weight ratio of 3:1:1 (Table 3). It has been confirmed efficacious in preventing respiratory tract diseases (Song et al., 2013). Total glycoside of Yupingfeng (YPF-G), a mixture extracted from Yupingfeng, have anti-inflammatory, immunoregulatory (Gao et al., 2009) and anti-fibrotic activities (Li

et al., 2015b). In a set of experiments, the authors showed that YPF-G containing astragaloside II and IV, could effectively attenuate the alveolitis and fibrosis induced by BLM, reduce the loss of body weight and increase of lung index, decrease the levels of Hyp, laminin, hyaluronic acid and Col-I, and down-regulate the over-expression of TGF-β1, inflammatory cytokine high-mobility group box 1 (HMGB1), and mesenchymal markers vimentin and α-SMA, but inhibited the decreased epithelial marker E-cadherin expression (Li et al., 2015b; Cui et al., 2015). The authors also showed the anti-fibrotic effect of total polysaccharides of Yupingfeng (YPF-P) by reducing α-SMA-positive cells, TGF-β1 expression and the synthesis of Col-I, on BLM-induced rats (Xu et al., 2014). These data suggest the therapeutic potential of Yupingfeng extracts (YPF-G and YPF-P) for PF, which were contributed to alleviating HMGB1 activity (Li et al., 2015b; Cui et al., 2015), TGF-β1 activation (Li et al., 2015b; Xu et al., 2014), as well as reversing EMT (Cui et al., 2015) (Table 4). Notwithstanding, the effects of Yupingfeng and its extracts have not been clarified in clinical and there is a need to fill in the blank.

Gao and partners carried out consequent studies to examine the anti-fibrotic effects and associated mechanisms of total glucosides of Danggui-Buxue-Tang (DBTG) on BLM-triggered pulmonary injury and fibrosis in rats (Gao et al., 2011, 2012; Zhao et al., 2015b). As shown in the studies, DBTG administration attenuated BLM-induced alveolitis and lung fibrosis (Gao et al., 2011, 2012; Zhao et al., 2015b), markedly reduced the weight loss and lung index (Gao et al., 2011), decreased the elevated levels of hyaluronic acid, laminin, type III procollagen, Col-IV (Gao et al., 2012), Col-I (Gao et al., 2011; Zhao et al., 2015b), TNF-α (Gao et al., 2011), TGF-β1 (Gao et al., 2011; Zhao et al., 2015b) and α-SMA (Zhao et al., 2015b), and decreased the mRNA levels of MMP-9 and TIMP-1 (Gao et al., 2012). For oxidative stress indicators, DBTG restrained BLM-induced expression of NOX4, and blunted the decline in SOD activity, T-AOC, as well as the increase of MDA and 8-isoprostaglandin in lung homogenates (Zhao et al., 2015b). These findings provide evidence that DBTG may serve as a promising candidate to prevent lung fibrosis, which action may be attributed to the reduction of pro-inflammatory cytokines and ECM deposition, balancing the MMP-9/TIMP-1 system, and inhibiting NOX4 to control the level of oxidative stress (Table 4). Nevertheless, the bioactive glucosides included in DBTG are still unknown and whether Danggui-Buxue-Tang and DBTG are effective in identified PF patients need to be proved with further investigations.

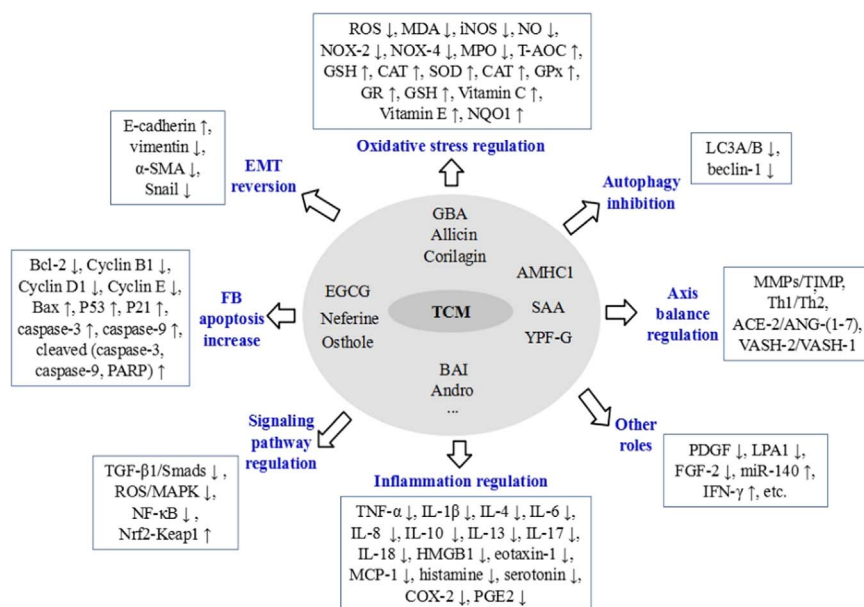


Fig. 2. Emerging studies have shown the anti-fibrotic effects of the bioactive ingredients from TCM. The inflammatory cytokines release, oxidative stress, cell apoptosis, autophagy, EMT, several signaling pathways as well as other mediators are involved.

7. Future investigations of TCM in PF therapy

PF sufferers generally undergo the patchy parenchymal inflammation, the reactive epithelial hyperplasia along with the transdifferentiation of FB to MFb, the formation of FB foci, basement membrane destruction, AEC apoptosis and excessive accumulation of ECM components (Rajasekaran et al., 2015; Li et al., 2014a). Such diseases in humans are burdened by high incidence and mortality. Nevertheless, a number of therapies have been shown to be effective in animal studies to minimize damage, but to date no “magic bullet” has been widely recognized. At present, the only effective therapy for lung fibrosis in the clinical is lung transplantation but with significant risks and complications. Recently, a new drug pirfenidone has been approved for clinical use, however, it has only been able to slow the progression of the disease with unproven safety of long-term use (King et al., 2014; Lancaster et al., 2016). Thus, extensive efforts are still urgent need to develop novel strategies to prevent or cure PF.

As is known to all, the natural products of TCM provide a vast source for the discovery of new drugs, thus exploring these medicines may provide novel strategies for blocking fibrosis development. Moreover, the accepted knowledge of TCM should be its less side effects and wide range of pharmacological activities (Hu et al., 2015; Shimizu et al., 2013; Wang et al., 2007; Wang and Ren, 2014). Nowadays, accumulating data have shown that TCM as well as its bioactive extracts may offer an opportunity to identify new anti-fibrotic compounds. In the present review, we expound the laboratory and clinical advance of the active agents from single herb and TCM formulas in the treatment of PF, as shown in the Tables. As reported in considerable work, these bioactive extracts display defensive role against PF by repressing the abnormal activation signaling pathways (ROS/MAPK, TGF- β 1/Smads, ACE-2/ANG(1–7), etc.) and regulating other associated mediators such as PDGF and HMGB1 (Fig. 2).

Over years, a number of animal PF models have been developed, and it provides important insights to understand the evolution of lung fibrosis and identify key cells, mediators, as well as the role of potential drugs based on molecular targets. The investigators have provided cumulative evidence of the protective role of TCM on PF in the models. There are also a fair number of clinical trials in PF using herbal medicines. From the collected data, these work are mostly published in Chinese language and some trials have methodological limitation and inconsistent identification of PF patients. Moreover, the conducted clinical trials only enroll dozens of patients and the clinical effects often combined with the Western medicines (mostly the glucocorticoids) as an adjuvant therapy by alleviating the PF symptoms or side effects without enough quantitative measurements, even some indicators were from the questionnaire and the dosage was not clearly provided. As the clinical researches of herb extracts are complex and some of which may have no bioactive or synergetic effects, the selected doses in clinical studies may be not enough to produce the best results. Thus, identification of the active constituents of herbs or the collaborative ingredients becomes a difficult but necessary task.

To better clarify the effectiveness of TCM and develop traditional medicines, the following concerns should be on the agenda:

First, the varied origin of herbs are often accompanied with different content of bioactive ingredients, so the use of genuine regional herbs on the related studies should be encouraged, and then the accumulated data of the same herb would be more valuable for an in-depth study. Besides, the methods to extract and analyze the active agents of TCM in different research groups or individuals are not always the same, particularly when studying the total extracts obtained from TCM which are extracted by different methods. Further, one major limitation of investigating the role of multi-components in TCM on PF is that the studies rarely specify which of the herbal compounds carry the main biological effect. Thus, the compared work between the total extracts of TCM and its potential active agents need to be conducted, from which we may distinguish the efficacy ingredients or

the synergistic effects focusing on PF. Besides, the data are mostly positive effects and lack of herb toxicology researches. To partly circumvent the weaknesses, above critical recommendations should be paid attention and more trials should be designated.

Second, TCM and its active agents often exert protective role on PF via a plurality of targets as proven, which may be unlike that of chemical drugs. On the one hand, the anti-fibrotic agents of TCM with multi-targets may be a major advantage because the pathogenesis of PF involves a variety of mechanisms (inflammation, oxidative stress, cell apoptosis, etc.) and potential targets (TGF- β 1, TNF- α , INF- γ , MMP-2, etc.). On the other hand, this event may mean more side effects due to the double-sided role of some targets in the progression of human diseases and health maintenance. However, herbal remedies have been used since ancient times, more often than not, some experimental data have shown that TCM sometimes have fewer adverse effects (Hu et al., 2015; Wang and Ren, 2014). The *in vitro* studies were mainly used for excavating the mechanisms of the extracts and their role is far from enough to present the true effects *in vivo*. In the light of these concerns, it should be an important part and more convincing to observe the affection for other organs or the whole body when exploring the anti-fibrotic effects of TCM in the lung.

Third, the pharmacological actions of TCM and the active agents in the researches of PF are not fully clarified, and the comprehensive evaluation in terms of the preclinical efficacy, optimal dose, toxicity evaluation and route of administration are still in its infancy. In addition, the mechanisms underlying the observed beneficial effects are widely unclear and their detailed investigation is challenging, especially the effective TCM formulas in clinical with few laboratory data, such as Huqi Huoxue decoction, Huaxian formula, Bufe Huoxue decoction and Qingjin decoction (Cheng, 2015; Wong and Ma, 2011; Wu and Zhang, 2010; Zhang et al., 2014a). Even if there are studies exploring considerable mechanisms, they neglect to observe the impact of these agents on the quality of animal life including the respiratory function, body weight, appearance and lifetime, which are the most basic but important clinical outcomes for the therapy of PF patients. The functional analysis of fibrotic lungs after the treatment of TCM as well as the active agents should be performed in experiments based on the successfully established PF models. More often than not, the associated studies lack the discussion of the experimental results and the ideas for further researches. Besides, the neglect in validating the experimental reagents (specifically cell lines and antibodies), inappropriate experimental design and execution, investigators' bias, and misuse of statistical procedures are major causes of data irreproducibility (Mullane and Williams, 2015a; Mullane et al., 2015b). These drawbacks undoubtedly contribute to the slow development of Chinese herb medicine in PF. Therefore, it will be extremely demanding to enrich the studies from the research design to perform conclusive mechanistic analysis on these medications.

Fourth, the application of animal models has provided critical insights in understanding the pathogenesis of PF and the development of potential drugs. It has shown that BLM, irradiation and LPS are commonly used inducers of PF in animals, whereas BLM plays a major role. In clinical, BLM is effectively against broad spectrum of cancers, but its use is often limited due to the main detrimental effects of inducing PF on patients (Guo et al., 2016). Thus, BLM is considered to be an ideal tool for imitating lung fibrosis. It can be administered intraperitoneally, intravenously, subcutaneously or intratracheally but intravenous (iv) and intratracheal (it) are the more commonly used routes. Notably, there are emerging concerns about BLM model regarding its high reproducibility and the ability to mimic the PF-like phenotypes and histologic features observed in patients treated with BLM. This PF model can be divided into three stages including injury, inflammation and fibrosis (Mouratis and Aidinis, 2011). BLM administration (often starting early within -1 to 0 days before the potential drugs treatment) may show effects on fibrosis due to anti-inflammatory activity within two weeks, while the followed fibrotic events appear only

between the third and fourth week (Della Latta et al., 2015). Unfortunately, in the murine model, lung fibrosis appears between 14 and 28 days after a single-dose administration of BLM, but the lung repairs itself and minimal to no evidence of fibrosis remains within 6 weeks (Degryse et al., 2010). Moreover, human PF is a chronic pathological process where epithelial injury, inflammation, mal-regeneration and fibrosis co-exist, and the result of repeated insults to the alveolar epithelium ultimately cause progressive and irreversible fibrosis, which is not parallel to animal models (Hau et al., 2010; Mouratis and Aidinis, 2011; Raghu et al., 2006).

These events mean that BLM model can only partially recapitulate PF and maybe not ideal for long-term studies. Furthermore, a majority of the herbs are administrated in the early period of BLM-induced inflammation rather than in the phase of formed PF, in other words, it is not clear whether the reported 'anti-fibrotic' effects are due to true inhibition of fibrosis or rather the result of reduced lung inflammation. It may be one reason that only very few experimental studies of potential drugs eventually into the clinical applications. Fortunately, the investigated agents of TCM and "Western drugs" in the emerging studies may have shown potential protective role, at least, on cancer patients that suffer from the adverse effects of BLM, which is also meaningful. As different models have varied processes of PF-like changes and the periods of successful establishment of PF is not the same yet. The animal models cannot truly mimic the general situations of human diseases including PF, but such models indeed provide accumulated evidence for further survey of the effective or toxic roles in clinical. In future studies, more exploration of TCM and the active agents on the formed PF models is urgent need. Furthermore, alternative or combined models of PF should be recruited to confirm the pharmaceutical property of the active agents of TCM for supplement, either by chemical induction or using transgenic animals (Kugler et al., 2016; Moore and Hogaboam, 2008).

Fifth, in view of the similar pathological mechanisms of tissue fibrosis, it can be noted that these TCM, which is effectively used for PF, may have benefits on other fibrotic disorders. Tissue fibrosis shares the core features including epithelial and endothelial injury and dysfunction, abnormal proliferation of MFb, smooth muscle cells and stellate cells, ECM deposition, and immune cell recruitment (Li et al., 2014b). A variety of identical cytokines (such as TNF- α and HMGB1), growth factors (such as TGF- β 1), and angiogenic factors (such as VEGF) have been confirmed to regulate the fibrogenesis in diverse organ systems including liver, kidney, lung, and myocardial. Thus, it is tempting to identify the pharmacological activities of these potential active agents in single herbs and TCM formulations on other organ fibrosis by the correlative mechanisms of PF, all of which are aimed to look for effective anti-fibrotic drugs.

Last but not least, in light of the complicated ingredients of TCM, especially the herbal formulations, exploring the potential agents against PF is a daunting work. Above all, if the ingredient is a monomer from TCM, we need to first provide enough evidence to prove its anti-fibrotic role in the animal and/or cell models. To enhance the benefits and weaken the side effects, appropriate structural improvement of potential effective agents from TCM might be of certain value, and then the comparative experiments should be carried out among the derivatives. In the present review, we have shown the effective monomers from single herbs, including naringin, glycyrrhizic acid, curcumin, etc., which are classified by their special structures and thus may be helpful for further design of these agents in developing innovative drugs for PF treatment. Meanwhile, if the anti-fibrotic agents is a mixture from TCM, we need to conduct a series of work for comparing the activities of the two monomers, one definite monomer to the total extracts or whole formula, as well as several definite monomers with different ratio, etc., based on the enriched signaling pathways involved in PF. Here, to guide these pharmacologic work, the "network pharmacology" strategies is urgent needed (Poornima et al., 2016; Zhou et al., 2016a).

Currently, the pharmacologic dogma, "single drug, single target,

single disease", is at the root of the lack of drug productivity. Low drug productivity has been a significant problem for several decades even though numerous novel technologies were introduced during this period (Poornima et al., 2016). From a systems biology viewpoint, "network pharmacology", a hot spot that is utilized to construct the bioactive ingredient-target networks of herbs, is particularly suitable for the investigations of the bioactivity spectrum of TCM and the underlying mechanisms in PF (Ke et al., 2016; Qi et al., 2016; Wei et al., 2016). Therefore, to elucidate the pharmacological characteristics and mechanism of action of the formulas such as Hu-qi-yin, Shenlong Decoction, Decoction for Strengthening Qi and Replenishing Lung, and Sho-seiryu-to, more studies should be conducted on the effects and chemical profiles (including bioactive ingredients) to investigate the network of the role in the prevention and cure of PF before the follow-up trails in large amount of PF patients. Besides, combining these perspectives with the new era of genetic modifiers identification may provide new insights into potential drugs for treating the severity of the fibrotic lung disease (Gu et al., 2009).

8. Conclusion

The collected data have shown the therapeutic benefits of TCM on PF, and TCM may serve as an essential supplement for the treatment strategy of PF. However, more continued work should be undertaken to clarify the unconfirmed chemical composition and regulatory mechanisms, conduct standard clinical trials, and evaluate the possible side effects. The research progress and views provided in this review will be helpful for future exploration of TCM in the development of PF therapy, and gain more reliable and reproducible data.

Conflicts of interest

None of the authors has any conflicts of interest to declare.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (Grant no. 81503129) and Traditional Chinese Medicine Research Project of Zhejiang Province (Grant no. 2013ZB085). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

- Aggarwal, B.B., Harikumar, K.B., 2009. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. *Int. J. Biochem. Cell Biol.* 41, 40–59.
- Akgedik, R., Akgedik, Ş., Karamanli, H., Uysal, S., Bozkurt, B., Ozol, D., Armutcu, F., Yıldırım, Z., 2012. Effect of resveratrol on treatment of bleomycin-induced pulmonary fibrosis in rats. *Inflammation* 35, 1732–1741.
- Ali, E.N., Mansour, S.Z., 2011. Boswellic acids extract attenuates pulmonary fibrosis induced by bleomycin and oxidative stress from gamma irradiation in rats. *Chin. Med.* 6, 36.
- Ashry, N.A., Gameil, N.M., Suddek, G.M., 2013. Modulation of cyclophosphamide-induced early lung injury by allicin. *Pharm. Biol.* 51, 806–811.
- Avasarala, S., Zhang, F., Liu, G., Wang, R., London, S.D., London, L., 2013. Curcumin modulates the inflammatory response and inhibits subsequent fibrosis in a mouse model of viral-induced acute respiratory distress syndrome. *PLoS One* 8, e57285.
- Baowen, Q., Yulin, Z., Xin, W., Wenjing, X., Hao, Z., Zhizhi, C., Xingmei, D., Xia, Z., Yuquan, W., Lijuan, C., 2010. A further investigation concerning correlation between anti-fibrotic effect of liposomal quercetin and inflammatory cytokines in pulmonary fibrosis. *Eur. J. Pharmacol.* 642, 134–139.
- Bardou, O., Menou, A., François, C., Duitman, J.W., von der Thüsen, J.H., Borie, R., Sales, K.U., Mutze, K., Castier, Y., Sage, E., Liu, L., Bugge, T.H., Fairlie, D.P., Königshoff, M., Crestani, B., Borensztajn, K.S., 2016. Membrane-anchored serine protease matriptase is a trigger of pulmonary fibrogenesis. *Am. J. Respir. Crit. Care Med.* 193, 847–860.
- Behr, J., 2013. Evidence-based treatment strategies in idiopathic pulmonary fibrosis.

- Eur. Respir. Rev. 22, 163–168.
- Boskabady, M.H., Farkhondeh, T., 2016. Antiinflammatory, antioxidant, and immunological effects of *Crocus sativus* L. and its main constituents. *Phytother. Res.* 30, 1072–1094.
- Boskabady, M.H., Mohsenpoor, N., Takaloo, L., 2010. Antiasthmatic effect of *Nigella sativa* in airways of asthmatic patients. *Phytomedicine* 17, 707–713.
- Brass, D.M., Spencer, J.C., Li, Z., Potts-Kant, E., Reilly, S.M., Dunkel, M.K., Latoche, J.D., Auten, R.L., Hollingsworth, J.W., Fattman, C.L., 2016. Retraction: innate immune activation by inhaled lipopolysaccharide, independent of oxidative stress, exacerbates silica-induced pulmonary fibrosis in mice. *PLoS One* 11, e0155388.
- Cabrera, S., Maciel, M., Herrera, I., Nava, T., Vergara, F., Gaxiola, M., López-Otin, C., Selman, M., Pardo, A., 2015. Essential role for the ATG4B protease and autophagy in bleomycin-induced pulmonary fibrosis. *Autophagy* 11, 670–684.
- Chang, C.C., Lee, Y.C., Lin, C.C., Chang, C.H., Chiu, C.D., Chou, L.W., Sun, M.F., Yen, H.R., 2016. Characteristics of traditional Chinese medicine usage in patients with stroke in Taiwan: a nationwide population-based study. *J. Ethnopharmacol.* 186, 311–321.
- Chaudhary, N.I., Roth, G.J., Hilberg, F., Müller-Quernheim, J., Prasse, A., Zissel, G., Schnapp, A., Park, J.E., 2007. Inhibition of PDGF, VEGF and FGF signalling attenuates fibrosis. *Eur. Respir. J.* 29, 976–985.
- Chen, C., Yang, S., Zhang, M., Zhang, Z., Hong, J., Han, D., Ma, J., Zhang, S.B., Okunieff, P., Zhang, L., 2016a. Triptolide mitigates radiation-induced pulmonary fibrosis via inhibition of axis of alveolar macrophages-NOXes-ROS-myofibroblasts. *Cancer Biol. Ther.* 17, 381–389.
- Chen, F., Wang, P.L., Fan, X.S., Yu, J.H., Zhu, Y., Zhu, Z.H., 2016b. Effect of Renshen Pingfei decoction, a traditional Chinese prescription, on IPF induced by bleomycin in rats and regulation of TGF- β 1/Smad3. *J. Ethnopharmacol.* 186, 289–297.
- Chen, G.H., Liu, Y.Q., 2013. Observation on clinical effect of andrographolide sulfonate nebulization in treating acute exacerbation of COPD. *China Pharm.* 22, 29–30.
- Chen, Y., Nie, Y.C., Luo, Y.L., Lin, F., Zheng, Y.F., Cheng, G.H., Wu, H., Zhang, K.J., Su, W.W., Shen, J.G., Li, P.B., 2013. Protective effects of naringin against paraquat-induced acute lung injury and pulmonary fibrosis in mice. *Food Chem. Toxicol.* 58, 133–140.
- Cheng, H.R., 2015. Study the efficacy of combine traditional Chinese and Western medicine to improve the quality life in patients with radiation-induced pulmonary fibrosis. *Med. Innov. China* 12, 103–105.
- Cho, I.H., Choi, Y.J., Gong, J.H., Shin, D., Kang, M.K., Kang, Y.H., 2015. Astragalosin inhibits autophagy-associated airway epithelial fibrosis. *Respir. Res.* 16, 51.
- Craig, V.J., Zhang, L., Hagood, J.S., Owen, C.A., 2015. Matrix metalloproteinases as therapeutic targets for idiopathic pulmonary fibrosis. *Am. J. Respir. Cell Mol. Biol.* 53, 585–600.
- Cui, W., Li, L., Li, D., Mo, X., Zhou, W., Zhang, Z., Xu, L., Zhao, P., Qi, L., Li, P., Gao, J., 2015. Total glucosides of Yupingfeng protects against bleomycin-induced pulmonary fibrosis in rats associated with reduced high mobility group box 1 activation and epithelial-mesenchymal transition. *Inflamm. Res.* 64, 953–961.
- Degryse, A.L., Tanjore, H., Xu, X.C., Polosukhin, V.V., Jones, B.R., McMahon, F.B., Gleaves, L.A., Blackwell, T.S., Lawson, W.E., 2010. Repetitive intratracheal bleomycin models several features of idiopathic pulmonary fibrosis. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 299, L442–L452.
- Della Latta, V., Cecchetti, A., Del Ry, S., Morales, M.A., 2015. Bleomycin in the setting of lung fibrosis induction: from biological mechanisms to counteractions. *Pharmacol. Res.* 97, 122–130.
- Divya, T., Dineshbabu, V., Soumyakrishnan, S., Sureshkumar, A., Sudhandiran, G., 2016. Celastrol enhances Nrf2 mediated antioxidant enzymes and exhibits anti-fibrotic effect through regulation of collagen production against bleomycin-induced pulmonary fibrosis. *Chem. Biol. Interact.* 246, 52–62.
- Du, S., Li, H., Cui, Y., Yang, L., Wu, J., Huang, H., Chen, Y., Huang, W., Zhang, R., Yang, J., Chen, D., Li, Y., Zhang, S., Zhou, J., Wei, Z., Chow, N.T., 2012. Houttuynia cordata inhibits lipopolysaccharide-induced rapid pulmonary fibrosis by up-regulating IFN- γ and inhibiting the TGF- β 1/Smad pathway. *Int. Immunopharmacol.* 13, 331–340.
- Faghihzadeh, F., Adibi, P., Rafiei, R., Hekmatdoost, A., 2014. Resveratrol supplementation improves inflammatory biomarkers in patients with nonalcoholic fatty liver disease. *Nutr. Res.* 34, 837–843.
- Gao, J., Feng, L.J., Huang, Y., Li, P., Xu, D.J., Li, J., Wu, Q., 2012. Total glucosides of Danggui Buxue Tang attenuates bleomycin-induced pulmonary fibrosis via inhibition of extracellular matrix remodeling. *J. Pharm. Pharmacol.* 64, 811–820.
- Gao, J., Li, J., Shao, X., Jin, Y., Lv, X.W., Ge, J.F., Huang, Y., Zhang, L., Chen, L., 2009. Antiinflammatory and immunoregulatory effects of total glucosides of Yupingfeng powder. *Chin. Med. J.* 122, 1636–1641.
- Gao, J., Huang, Y., Li, P., Xu, D., Li, J., Liu, Y., Huang, Z., Wu, Q., Shao, X., 2011. Antifibrotic effects of total glucosides of Danggui-Buxue-Tang in a rat model of bleomycin-induced pulmonary fibrosis. *J. Ethnopharmacol.* 136, 21–26.
- Gao, L., Tang, H., He, H., Liu, J., Mao, J., Ji, H., Lin, H., Wu, T., 2015. Glycyrrhizic acid alleviates bleomycin-induced pulmonary fibrosis in rats. *Front. Pharmacol.* 6, 215.
- Gao, Y., Lu, J., Zhang, Y., Chen, Y., Gu, Z., Jiang, X., 2013. Baicalein attenuates bleomycin-induced pulmonary fibrosis in rats through inhibition of miR-21. *Pulm. Pharmacol. Ther.* 26, 649–654.
- Gao, Y., Yao, L.F., Zhao, Y., Wei, L.M., Guo, P., Yu, M., Cao, B., Li, T., Chen, H., Zou, Z.M., 2016. The Chinese herbal medicine formula mKG suppresses pulmonary fibrosis of mice induced by bleomycin. *Int. J. Mol. Sci.* 17, 238.
- Gholamnezhad, Z., Keyhanmanesh, R., Boskabady, M.H., 2015. Anti-inflammatory, antioxidant, and immunomodulatory aspects of *Nigella sativa* for its preventive and bronchodilatory effects on obstructive respiratory diseases: a review of basic and clinical evidence. *J. Funct. Foods* 17, 910–927.
- Gholamnezhad, Z., Havakhah, S., Boskabady, M.H., 2016. Preclinical and clinical effects of *Nigella sativa* and its constituent, thymoquinone: a review. *J. Ethnopharmacol.* 190, 372–386.
- Gu, X., Huang, N., Gu, J., Joshi, M.K., Wang, H., 2016. Employing observational method for prospective data collection: a case study for analyzing diagnostic process and evaluating efficacy of TCM treatments for diabetes mellitus. *J. Ethnopharmacol.* 192, 516–523.
- Gu, Y., Harley, I.T., Henderson, L.B., Aronow, B.J., Vietor, I., Huber, L.A., Harley, J.B., Kilpatrick, J.R., Langefeld, C.D., Williams, A.H., Jegga, A.G., Chen, J., Wills-Karp, M., Arshad, S.H., Ewart, S.L., Thio, C.L., Flick, L.M., Filippi, M.D., Grimes, H.L., Drumm, M.L., Cutting, G.R., Knowles, M.R., Karp, C.L., 2009. Identification of IFRD1 as a modifier gene for cystic fibrosis lung disease. *Nature* 458, 1039–1042.
- Guo, H., Zhang, Z., Su, Z., Sun, C., Zhang, X., Zhao, X., Lai, X., Su, Z., Li, Y., Zhan, J.Y., 2016. Enhanced anti-tumor activity and reduced toxicity by combination andrographolide and bleomycin in ascitic tumor-bearing mice. *Eur. J. Pharmacol.* 776, 52–63.
- Hao, Y., Liu, Y., 2016. Osthole alleviates bleomycin-induced pulmonary fibrosis via modulating angiotensin-converting enzyme 2/angiotensin-(1–7) axis and decreasing inflammation responses in rats. *Biol. Pharm. Bull.* 39, 457–465.
- Hau, D.K., Zhu, G.Y., Leung, A.K., Wong, R.S., Cheng, G.Y., Lai, P.B., Tong, S.W., Lau, F.Y., Chan, K.W., Wong, W.Y., Lam, K.H., Cheng, C.H., Cheung, F., Chui, C.H., Gambhari, R., Fong, D.W., 2010. In vivo anti-tumour activity of corilagin on Hep3B hepatocellular carcinoma. *Phytomedicine* 18, 11–15.
- He, H., Tang, H., Gao, L., Wu, Y., Feng, Z., Lin, H., Wu, T., 2015. Tanshinone IIA attenuates bleomycin-induced pulmonary fibrosis in rats. *Mol. Med. Rep.* 11, 4190–4196.
- Higdon, J.V., Frei, B., 2003. Tea catechins and polyphenols: health effects, metabolism, and antioxidant functions. *Crit. Rev. Food Sci. Nutr.* 43, 89–143.
- Hosseini, N., Cho, Y., Lockett, R.F., Kolliputi, N., 2015. The role of the NLRP3 inflammasome in pulmonary diseases. *Ther. Adv. Respir. Dis.* 9, 188–197.
- Hu, C., Wang, Y., Fan, Y., Li, H., Wang, C., Zhang, J., Zhang, S., Han, X., Wen, C., 2015. Lipidomics revealed idiopathic pulmonary fibrosis-induced hepatic lipid disorders corrected with treatment of baicalin in a murine model. *AAPS J.* 17, 711–722.
- Huang, T.T., Lai, H.C., Ko, Y.F., Ojcius, D.M., Lan, Y.W., Martel, J., Young, J.D., Chong, K.Y., 2015. *Hirsutiella sinensis* mycelium attenuates bleomycin-induced pulmonary inflammation and fibrosis in vivo. *Sci. Rep.* 5, 15282.
- Imai, Y., Kuba, K., Rao, S., Huan, Y., Guo, F., Guan, B., Yang, P., Sarao, R., Wada, T., Leong-Poi, H., Crackower, M.A., Fukamizu, A., Hui, C.C., Hein, L., Uhlir, S., Slutsky, A.S., Jiang, C., Penninger, J.M., 2005. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 436, 112–116.
- Jayakumar, T., Hsieh, C.Y., Lee, J.J., Sheu, J.R., 2013. Experimental and clinical pharmacology of andrographis paniculata and its major bioactive phytoconstituent andrographolide. *Evid. Based Complement. Altern. Med.* 2013, 846740.
- Ji, Y., Wang, T., Wei, Z.F., Lu, G.X., Xia, Y.F., Dai, Y., 2013. Paeoniflorin, the main active constituent of *Paeonia lactiflora* roots, attenuates bleomycin-induced pulmonary fibrosis in mice by suppressing the synthesis of type I collagen. *J. Ethnopharmacol.* 149, 825–832.
- Ji, Y., Dou, Y.N., Zhao, Q.W., Zhang, J.Z., Yang, Y., Wang, T., Xia, Y.F., Dai, Y., Wei, Z.F., 2016. Paeoniflorin suppresses TGF- β mediated epithelial-mesenchymal transition in pulmonary fibrosis through a Smad-dependent pathway. *Acta Pharmacol. Sin.* 37, 794–804.
- Jiang, L., Zhang, Y., 2015a. Clinical research of curcumin in the intervention treatment for pulmonary fibrosis induced by paraquat poisoning. *Med. Recapitul.* 21, 883–885.
- Jiang, S.P., Liang, R.Y., Yang, L., Zhang, Y., Lv, Z.Q., 2006. Effects of triptolide on serum cytokine levels, symptoms and pulmonary function in patients with steroid-resistant asthma. *Chin. J. Pathophysiol.* 22, 1571–1574.
- Jiang, X., Zhang, Y., Li, F., Zhu, Y., Chen, Y., Yang, S., Sun, G., 2015b. Allicin as a possible adjunctive therapeutic drug for stage II oral submucous fibrosis: a preliminary clinical trial in a Chinese cohort. *Int. J. Oral. Maxillofac. Surg.* 44, 1540–1546.
- Jin, Y., Khadka, D.B., Cho, W.J., 2016. Pharmacological effects of berberine and its derivatives: a patent update. *Expert Opin. Ther. Pat.* 26(16), 229–243.
- Kanter, M., 2009. Effects of *Nigella sativa* seed extract on ameliorating lung tissue damage in rats after experimental pulmonary aspirations. *Acta Histochem.* 111, 393–403.
- Ke, Z., Zhang, X., Cao, Z., Ding, Y., Li, N., Cao, L., Wang, T., Zhang, C., Ding, G., Wang, Z., Xu, X., Xiao, W., 2016. Drug discovery of neurodegenerative disease through network pharmacology approach in herbs. *Biomed. Pharmacother.* 78, 272–279.
- Keyhanmanesh, R., Gholamnezhad, Z., Boskabady, M.H., 2014. The relaxant effect of *Nigella sativa* on smooth muscles, its possible mechanisms and clinical applications. *Iran. J. Basic Med. Sci.* 17, 939–949.
- King, T.E., Jr., Bradford, W.Z., Castro-Bernardini, S., Fagan, E.A., Glaspole, I., Glassberg, M.K., Gorina, E., Hopkins, P.M., Kardatzke, D., Lancaster, L., Lederer, D.J., Nathan, S.D., Pereira, C.A., Sahn, S.A., Sussman, R., Swigris, J.J., Noble, P.W., ASCEND Study Group, 2014. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N. Engl. J. Med.* 370, 2083–2092.
- Kolosova, I., Nethery, D., Kern, J.A., 2011. Role of Smad2/3 and p38 MAP kinase in TGF- β 1-induced epithelial-mesenchymal transition of pulmonary epithelial cells. *J. Cell. Physiol.* 226, 1248–1254.
- Kuba, K., Imai, Y., Rao, S., Gao, H., Guo, F., Guan, B., Huan, Y., Yang, P., Zhang, Y., Deng, W., Bao, L., Zhang, B., Liu, G., Wang, Z., Chappell, M., Liu, Y., Zheng, D., Leibbrandt, A., Wada, T., Slutsky, A.S., Liu, D., Qin, C., Jiang, C., Penninger, J.M., 2015. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat. Med.* 11, 875–879.
- Kugler, J., Luch, A., Oelgeschläger, M., 2016. Transgenic mouse models transferred into the test tube: new perspectives for developmental toxicity testing in vitro? *Trends Pharmacol.* 37, 822–830.

- Lam, T.K., Rotunno, M., Lubin, J.H., Wacholder, S., Consonni, D., Pesatori, A.C., Bertazzi, P.A., Chanock, S.J., Burdette, L., Goldstein, A.M., Tucker, M.A., Caporaso, N.E., Subar, A.F., Landi, M.T., 2010. Dietary quercetin, quercetin-gene interaction, metabolic gene expression in lung tissue and lung cancer risk. *Carcinogenesis* 31, 634–642.
- Lancaster, L., Albera, C., Bradford, W.Z., Costabel, U., du Bois, R.M., Fagan, E.A., Fishman, R.S., Glaspole, I., Glassberg, M.K., King, T.E., Jr., Lederer, D.J., Lin, Z., Nathan, S.D., Pereira, C.A., Swigris, J.J., Valeyre, D., Noble, P.W., 2016. Safety of pirfenidone in patients with idiopathic pulmonary fibrosis: integrated analysis of cumulative data from 5 clinical trials. *BMJ Open Respir. Res.* 3, e000105.
- Le Marchand, L., Murphy, S.P., Hankin, J.H., Wilkens, L.R., Kolonel, L.N., 2000. Intake of flavonoids and lung cancer. *J. Natl. Cancer Inst.* 92, 154–160.
- Lee, J.C., Kinniry, P.A., Arguiri, E., Serota, M., Kanterakis, S., Chatterjee, S., Solomides, C.C., Javvadi, P., Koumenis, C., Cengel, K.A., Christofidou-Solomidou, M., 2010. Dietary curcumin increases antioxidant defenses in lung, ameliorates radiation-induced pulmonary fibrosis, and improves survival in mice. *Radiat. Res.* 173, 590–601.
- Li, J., Wang, G.X., Tang, W.Z., Shi, J.F., Chen, F., 2014a. The effect observation of hydroxy safflor yellow A in the treatment of acute cerebral infarction. *Shandong Med. J.* 54, 65–67.
- Li, L., Li, D., Xu, L., Zhao, P., Deng, Z., Mo, X., Li, P., Qi, L., Li, J., Gao, J., 2015b. Total extract of Yupingfeng attenuates bleomycin-induced pulmonary fibrosis in rats. *Phytomedicine* 22, 111–119.
- Li, L.C., Gao, J., Li, J., 2014a. Emerging role of HMGB1 in fibrotic diseases. *J. Cell. Mol. Med.* 18, 2331–2339.
- Li, L.C., Li, J., Gao, J., 2014b. Functions of galectin-3 and its role in fibrotic diseases. *J. Pharmacol. Exp. Ther.* 351, 336–343.
- Li, L.C., Li, D.L., Xu, L., Mo, X.T., Cui, W.H., Zhao, P., Zhou, W.C., Gao, J., Li, J., 2015a. High-mobility group box 1 mediates epithelial-to-mesenchymal transition in pulmonary fibrosis involving transforming growth factor- β /Smad2/3 signaling. *J. Pharmacol. Exp. Ther.* 354, 302–309.
- Li, L.S., 2004. Large dose of fresh *Eclipta prostrata* in combination with a small amount of *citrus reticulata Blanco* peels in the treatment of 50 cases chronic bronchitis. *J. Tradit. Chin. Med.* 45, (92–92).
- Li, S., Wang, R., Zhang, Y., Zhang, X., Layon, A.J., Li, Y., Chen, M., 2006. Symptom combinations associated with outcome and therapeutic effects in a cohort of cases with SARS. *Am. J. Chin. Med.* 34, 937–947.
- Li, X.D., Zhang, J.L., Wang, C., Zheng, S.L., 2015c. The clinical research of curative effect of *Cordyceps sinensis* extract combined with methylprednisolone on with idiopathic pulmonary fibrosis. *Acta Acad. Med. Weifang* 37, 29–31.
- Lien, A.S., Jiang, Y.D., Mou, C.H., Sun, M.F., Gau, B.S., Yen, H.R., 2016. Integrative traditional Chinese medicine therapy reduces the risk of diabetic ketoacidosis in patients with type 1 diabetes mellitus. *J. Ethnopharmacol.* 191, 324–330.
- Lin, C.Y., 2015. Clinical observation of *Eriobotrya japonica* (Thunb.) Lindl. leaf drink in the treatment of the gastrointestinal side effects of middle-late stage lung cancer chemotherapy. *Shandong J. Tradit. Chin. Med.* 34, 178–179.
- Liu, H., Fang, S., Wang, W., Cheng, Y., Zhang, Y., Liao, H., Yao, H., Chao, J., 2016. Macrophage-derived MCP1 mediates silica-induced pulmonary fibrosis via autophagy. *Part. Fibre Toxicol.* 13, 55.
- Liu, L., Lu, W., Ma, Z., Li, Z., 2012. Oxymatrine attenuates bleomycin-induced pulmonary fibrosis in mice via the inhibition of inducible nitric oxide synthase expression and the TGF- β /Smad signaling pathway. *Int. J. Mol. Sci.* 29, 815–822.
- Liu, L., Li, J., Zhang, Y., Zhang, S., Ye, J., Wen, Z., Ding, J., Kunapuli, S.P., Luo, X., Ding, Z., 2014. Salvianolic acid B inhibits platelets as a P2Y₁₂ antagonist and PDE inhibitor: evidence from clinic to laboratory. *Thromb. Res.* 134, 866–876.
- Liu, Z.M., Sang, L.L., Sun, P., Liu, Z.H., Xu, Q.H., 2015. Effects of resveratrol on the lung functions, serum TNF- α and IL-8 in women patients with chronic obstructive pulmonary disease. *Guangdong Med. J.* 36, 2531–2533.
- Lu, X.D., Pang, L.J., Wang, L.L., Nan, M.H., Ma, Z., 2010. Effects of Chinese herbal medicine Shenlong Decoction on mRNA expressions of matrix metalloproteinase-2 and tissue inhibitor of metalloproteinase-1 in lung tissue of rats with pulmonary fibrosis induced by bleomycin. *Zhong Xi Yi Jie He Xue Bao* 8, 961–967.
- Mei, X.L., 2014. Effect of Runfei decoction on radiation pneumonitis and radioactive pulmonary fibrosis of patients with lung cancer. *China J. Chin. Med.* 29, 177–179.
- Minegishi, Y., Sudoh, J., Kuribayashi, H., Mizutani, H., Seike, M., Azuma, A., Yoshimura, A., Kudoh, S., Gemma, A., 2011. The safety and efficacy of weekly paclitaxel in combination with carboplatin for advanced non-small cell lung cancer with idiopathic interstitial pneumonias. *Lung Cancer* 71, 70–74.
- Ming, L.J., Yin, A.C., 2013. Therapeutic effects of glycyrrhizic acid. *Nat. Prod. Commun.* 8, 415–418.
- Moore, B.B., Hogaboam, C.M., 2008. Murine models of pulmonary fibrosis. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 294, L152–L160.
- Mouratis, M.A., Aidinis, V., 2011. Modeling pulmonary fibrosis with bleomycin. *Curr. Opin. Pulm. Med.* 17, 355–361.
- Mullane, K., Williams, M., 2015a. Unknown unknowns in biomedical research: does an inability to deal with ambiguity contribute to issues of irreproducibility? *Biochem. Pharmacol.* 97, 133–136.
- Mullane, K., Enna, S.J., Piette, J., Williams, M., 2015b. Guidelines for manuscript submission in the peer-reviewed pharmacological literature. *Biochem. Pharmacol.* 97, 225–235.
- Nikbakht, J., Hemmati, A.A., Arzi, A., Mansouri, M.T., Rezaie, A., Ghafourian, M., 2015. Protective effect of gallic acid against bleomycin-induced pulmonary fibrosis in rats. *Pharmacol. Rep.* 67, 1061–1067.
- Niu, C.H., Wang, Y., Liu, J.D., Wang, J.L., Xiao, J.H., 2013a. Protective effects of neferine on amiodarone-induced pulmonary fibrosis in mice. *Eur. J. Pharmacol.* 714, 112–119.
- Niu, X.H., Hua, H.Y., Guo, W.J., Zhang, Y., Liu, M., Hong, Y., Wu, P.F., Lu, P., Zhang, H.F., 2013b. Clinical efficiency of tanshinone IIA-sulfonate in treatment of liver fibrosis of advanced schistosomiasis. *Chin. J. Schisto. Control* 25, 137–140.
- Notarnicola, A., Tafuri, S., Fusaro, L., Moretti, L., Pesce, V., Moretti, B., 2011. The “MESACA” study: methylsulfonylmethane and boswellic acids in the treatment of gonarthrosis. *Adv. Ther.* 28, 894–906.
- Pan, Y., Fu, H., Kong, Q., Xiao, Y., Shou, Q., Chen, H., Ke, Y., Chen, M., 2014. Prevention of pulmonary fibrosis with salvianolic acid A by inducing fibroblast cell cycle arrest and promoting apoptosis. *J. Ethnopharmacol.* 155, 1589–1596.
- Papiris, S.A., Kagouridis, K., Kolilekas, L., Triantafyllidou, C., Tsangaris, I., Manali, E.D., 2012. Pirfenidone treatment in idiopathic pulmonary fibrosis: too much of a great expectation? *Eur. Respir. J.* 40, 794–795.
- Paterson, R.R., 2008. Cordyceps: a traditional Chinese medicine and another fungal therapeutic biofactory? *Phytochemistry* 69, 1469–1495.
- Peng, H.B., Wu, A.P., Liu, Y., Tian, J.L., Wang, J.X., 2013. Protectant effect of quercetin on the expression of matrix metalloproteinases in human embryonic lung fibroblasts in vitro. *Her. Med.* 32, 695–698.
- Poornima, P., Kumar, J.D., Zhao, Q., Blunder, M., Efferth, T., 2016. Network pharmacology of cancer: from understanding of complex interactomes to the design of multi-target specific therapeutics from nature. *Pharmacol. Res.* 111, 290–302.
- Prasad, J., Holland, A.E., Glaspole, I., Westall, G., 2016. Idiopathic pulmonary fibrosis: an Australian perspective. *Intern. Med. J.* 46, 663–668.
- Qi, Q., Li, R., Li, H.Y., Cao, Y.B., Bai, M., Fan, X.J., Wang, S.Y., Zhang, B., Li, S., 2016. Identification of the anti-tumor activity and mechanisms of nuciferine through a network pharmacology approach. *Acta Pharmacol. Sin.* 37, 963–972.
- Qu, Y., Zhang, G., Ji, Y., Zhua, H., Lv, C., Jiang, W., 2016. Protective role of gambogic acid in experimental pulmonary fibrosis in vitro and in vivo. *Phytomedicine* 23, 350–358.
- Raghu, G., Weycker, D., Edelsberg, J., Bradford, W.Z., Oster, G., 2006. Incidence and prevalence of idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 174, 810–816.
- Rajadurai, M., Prince, P.S.M., 2006. Preventive effect of naringin on lipid peroxides and antioxidants in isoproterenol-induced cardiotoxicity in Wistar rats: biochemical and histopathological evidences. *Toxicology* 228, 259–268.
- Rajasekaran, S., Rajaguru, P., Gandhi, P.S., 2015. MicroRNAs as potential targets for progressive pulmonary fibrosis. *Front. Pharmacol.* 6, 254.
- Rogliani, P., Calzetta, L., Cavalli, F., Matera, M.G., Cazzola, M., 2016. Pirfenidone, nintedanib and N-acetylcysteine for the treatment of idiopathic pulmonary fibrosis: a systematic review and meta-analysis. *Pulm. Pharmacol. Ther.* 40, 95–103.
- Scotton, C.J., Hayes, B., Alexander, R., Datta, A., Forty, E.J., Mercer, P.F., Blanchard, A., Chambers, R.C., 2013. Ex vivo micro-computed tomography analysis of bleomycin-induced lung fibrosis for preclinical drug evaluation. *Eur. Respir. J.* 42, 1633–1645.
- Shadkhan, Y., Shemesh, E., Mirelman, D., Miron, T., Rabinov, A., Wilchek, M., Osherov, N., 2004. Efficacy of allicin, the reactive molecule of garlic, in inhibiting *Aspergillus* spp. in vitro, and in a murine model of disseminated aspergillosis. *J. Antimicrob. Chemother.* 53, 832–836.
- Shakeri, F., Boskabady, M.H., 2015. A review of the relaxant effect of various medicinal plants on tracheal smooth muscle, their possible mechanism(s) and potency. *J. Ethnopharmacol.* 175, 528–548.
- Shi, X.Y., Hu, W.S., 1998. Effects of neferine on platelet aggregation in patients with hyperlipidemia and healthy subjects. *Chin. Pharmacol. Bull.* 14, 237–239.
- Shimizu, Y., Shimoyama, Y., Kawada, A., Kusano, M., Hosomi, Y., Sekiguchi, M., Kawata, T., Horie, T., Ishii, Y., Yamada, M., Dobashi, K., Takise, A., 2013. Gastrointestinal symptoms in idiopathic pulmonary fibrosis patients treated with pirfenidone and herbal medicine. *J. Biol. Regul. Homeost. Agents* 28, 433–442.
- Smith, M.R., Gangireddy, S.R., Narala, V.R., Hogaboam, C.M., Standiford, T.J., Christensen, P.J., Kondapi, A.K., Reddy, R.C., 2010. Curcumin inhibits fibrosis-related effects in IPF fibroblasts and in mice following bleomycin-induced lung injury. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 298, L616–L625.
- Sohi, K.K., Mittal, N., Hundal, M.K., Khanduja, K.L., 2003. Gallic acid, an antioxidant, exhibits antiapoptotic potential in normal human lymphocytes: a Bcl-2 independent mechanism. *J. Nutr. Sci. Vitaminol.* 49, 221–227.
- Song, J., Li, J., Zheng, S.R., Jin, Y., Huang, Y., 2013. Anti-inflammatory and immunoregulatory effects of Yupingfeng powder on chronic bronchitis rats. *Chin. J. Integr. Med.* 19, 353–359.
- Sriram, N., Kalayarasan, S., Sudhandiran, G., 2009a. Epigallocatechin-3-gallate augments antioxidant activities and inhibits inflammation during bleomycin-induced experimental pulmonary fibrosis through Nrf2-Keap1 signaling. *Pulm. Pharmacol. Ther.* 22, 221–236.
- Sriram, N., Kalayarasan, S., Sudhandiran, G., 2009b. Epigallocatechin-3-gallate exhibits anti-fibrotic effect by attenuating bleomycin-induced glycoconjugates, lysosomal hydrolases and ultrastructural changes in rat model pulmonary fibrosis. *Chem. Biol. Interact.* 180, 271–280.
- Sriram, N., Kalayarasan, S., Manikandan, R., Arumugam, M., Sudhandiran, G., 2015. Epigallocatechin gallate attenuates fibroblast proliferation and excessive collagen production by effectively intervening TGF- β 1 signalling. *Clin. Exp. Pharmacol. Physiol.* 42, 849–859.
- Sun, G.X., 2016. Efficacy and safety of safflower yellow sodium chloride injection combined with methylprednisolone in treatment of patients with idiopathic pulmonary fibrosis. *J. Clin. Med. Pract.* 20, 46–49.
- Sun, Z.T., Feng, J.H., Li, X.J., Lian, F., Liu, E.S., 2008. Interference of Tonifying Qi, activating blood and dispersing accumulation on pulmonary fibrosis and the mechanism research. *J. Tianjin Univ. Tradit. Chin. Med.* 27, 209–212.
- Tang, H., Gao, L., Mao, J., He, H., Liu, J., Cai, X., Lin, H., Wu, T., 2016. Salidroside protects against bleomycin-induced pulmonary fibrosis: activation of Nrf2-antioxidant signaling, and inhibition of NF- κ B and TGF- β 1/Smad2/-3 pathways.

- Cell Stress Chaperones 21, 239–249.
- Tanno, Y., Kakuta, Y., Aikawa, T., Shindoh, Y., Ohno, I., Takishima, T., 1988. Effects of Qing-Fei-Tang (Seihai-to) and baicalein, its main component flavonoid, on lucigenin-dependent chemiluminescence and leukotriene-dependence chemiluminescence and leukotriene B₄ synthesis of human alveolar macrophages. *Am. J. Chin. Med.* 16, 145–154.
- Tarning, J., 2016. Treatment of malaria in pregnancy. *N. Engl. J. Med.* 374, 981–982.
- Tian, T.D., Yang, F., Tang, J.W., Niu, H., Gao, Q.L., Pei, J.W., 2014. Effect of Qingre Huoxue Sanjie Chinese medicine compound on serum cytokines IL-6, TNF- α , TGF- β 1 level of radiation pneumonitis and pulmonary fibrosis patients. *Chin. J. Exp. Tradit. Med. Formulae* 20, 127–130.
- Turgut, N.H., Kara, H., Elagoz, S., Devenci, K., Gungor, H., Arslanbas, E., 2016. The protective effect of naringin against bleomycin-induced pulmonary fibrosis in Wistar rats. *Pulm. Med.* 2016, 7601393.
- Wang, C., Song, X., Li, Y., Han, F., Gao, S., Wang, X., Xie, S., Lv, C., 2013. Low-dose paclitaxel ameliorates pulmonary fibrosis by suppressing TGF- β 1/Smad3 pathway via mir-140 upregulation. *PLoS One* 8, e70725.
- Wang, K., Ren, X.L., 2014a. Curative effect of Yangyin Yiqi formula in treating pulmonary fibrosis. *Shaanxi J. Tradit. Chin. Med.* 35, 182–183.
- Wang, L., 2012. Effects of glycyrrhizic acid diamine on serum hyaluronic acid and procollagen III in patients with idiopathic pulmonary interstitial fibrosis. *Pract. J. Card. Cereb. Pneumal Vasc. Dis.* 20, 641–642.
- Wang, L., Jin, M., Zang, B.X., Wu, Y., 2011a. Inhibitory effect of safflor yellow on pulmonary fibrosis. *Biol. Pharm. Bull.* 34, 511–516.
- Wang, S.F., Zhao, L., 2016. Twenty-eight cases of silicosis combined with cor pulmonale treated with salvia miltiorrhiza polyphenols acid salt. *Henan Tradit. Chin. Med.* 6, 1112–1113.
- Wang, X., Morris-Natschke, S.L., Lee, K.H., 2007. New developments in the chemistry and biology of the bioactive constituents of tanshen. *Med. Res. Rev.* 27, 133–148.
- Wang, Y., Xue, C., Dong, F., Peng, Y., Zhang, Y., Jin, M., Zang, B., Tan, L., 2014b. Hydroxysafflor yellow A attenuates small airway remodeling in a rat model of chronic obstructive pulmonary disease. *Biol. Pharm. Bull.* 37, 1591–1598.
- Wang, Y.P., Zhao, W., Xue, R., Zhou, Z.X., Liu, F., Han, Y.X., Ren, G., Peng, Z.G., Cen, S., Chen, H.S., Li, Y.H., Jiang, J.D., 2011b. Oxymatrine inhibits hepatitis B infection with an advantage of overcoming drug-resistance. *Antivir. Res.* 89, 227–231.
- Wang, Z., Guo, Q.Y., Zhang, X.J., Li, X., Li, W.T., Ma, X.T., Ma, L.J., 2014c. Corilagin attenuates aerosol bleomycin-induced experimental lung injury. *Int. J. Mol. Sci.* 15, 9762–9779.
- Wei, S., Niu, M., Wang, J., Wang, J., Su, H., Luo, S., Zhang, X., Guo, Y., Liu, L., Liu, F., Zhao, Q., Chen, H., Xiao, X., Zhao, P., Zhao, Y., 2016. A network pharmacology approach to discover active compounds and action mechanisms of San-Cao granule for treatment of liver fibrosis. *Drug Des. Dev. Ther.* 10, 733–743.
- White, E.S., Xia, M., Murray, S., Dyal, R., Flaherty, C.M., Flaherty, K.R., Moore, B.B., Cheng, L., Doyle, T.J., Villalba, J., Dellaripa, P.F., Rosas, I.O., Kurtis, J.D., Martinez, F.J., 2016. Plasma surfactant protein-D, matrix metalloproteinase-7, and osteopontin index distinguishes idiopathic pulmonary fibrosis from other idiopathic interstitial pneumonias. *Am. J. Respir. Crit. Care Med.* 194, 1242–1251.
- Wollin, L., Mailet, I., Quesniaux, V., Holweg, A., Ryffel, B., 2014. Antifibrotic and anti-inflammatory activity of the tyrosine kinase inhibitor nintedanib in experimental models of lung fibrosis. *J. Pharmacol. Exp. Ther.* 349, 209–220.
- Wollin, L., Wex, E., Pautsch, A., Schnapp, G., Hostettler, K.E., Stowasser, S., Kolb, M., 2015. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. *Eur. Respir. J.* 45, 1434–1445.
- Wong, H., Ma, D.F., 2011. Clinical research of Qingjin decoction in treating idiopathic pulmonary fibrosis. *Gansu J. TCM* 24, 40–41.
- Wu, H., Li, Y., Wang, Y., Xu, D., Li, C., Liu, M., Sun, X., Li, Z., 2014. Tanshinone IIA attenuates bleomycin-induced pulmonary fibrosis via modulating angiotensin-converting enzyme 2/angiotensin-(1-7) axis in rats. *Int. J. Med. Sci.* 11, 578–586.
- Wu, Z.H., Zhang, X.X., 2010. Clinical observation of Bufe Huoxue decoction in treating idiopathic pulmonary fibrosis. *Beijing J. Tradit. Chin. Med.* 29, 118–120.
- Xiao, J.H., Zhang, J.H., Chen, H.L., Feng, X.L., Wang, J.L., 2005. Inhibitory effects of isoliensinine on bleomycin-induced pulmonary fibrosis in mice. *Planta Med.* 71, 225–230.
- Xiao, Q.L., Du, Y.M., Liu, K.Q., Zhang, F., Wu, J., 2016. Effects of tanshinone IIA-sulfonate on C-reactive protein and procalcitonin in patients with severe pneumonia. *J. Clin. Med. Pract.* 20, 151–152.
- Xu, L., Li, L.C., Zhao, P., Qi, L.W., Li, P., Gao, J., Fei, G.H., 2014. Total polysaccharide of Yupingfeng protects against bleomycin-induced pulmonary fibrosis via inhibiting transforming growth factor- β 1-mediated type I collagen abnormal deposition in rats. *J. Pharm. Pharmacol.* 66, 1786–1795.
- Xu, S.C., 2016. Clinical observation of peony licorice decoction in treating patients with advanced cancer. *J. Liaoning Univ. TCM* 18, 183–185.
- Yang, C.Q., Sun, P.Y., Ding, D.Z., Moriuchi, H., Ishitsuka, Y., Irikura, M., Irie, T., 2010. The ethical Kampo formulation Sho-seiryu-to (TJ-19) prevents bleomycin-induced pulmonary fibrosis in rats. *Biol. Pharm. Bull.* 33, 1438–1442.
- Yang, J., 2014. A clinical study on treating idiopathic pulmonary fibrosis with Dazhu Hongjingian injection. *Clin. J. Chin. Med.* 6, (8–9).
- Yang, J., Cui, Y., Kolb, M., 2009. How useful is traditional herbal medicine for pulmonary fibrosis? *Respirology* 14, 1082–1091.
- Yang, Y., Li, J., Kang, J.B., 2012b. Clinical observation on the effect of Jade screen powder associated with hormone in the treatment of radiation-induced pulmonary fibrosis. *China Med. Her.* 9, 35–37.
- Yang, Y., Huang, Y., Huang, C., Lv, X., Liu, L., Wang, Y., Li, J., 2012a. Antifibrosis effects of triterpene acids of *Eriobotrya japonica* (Thunb.) Lindl. leaf in a rat model of bleomycin-induced pulmonary fibrosis. *J. Pharm. Pharmacol.* 64, 1751–1760.
- You, H., Wei, L., Sun, W.L., Wang, L., Yang, Z.L., Liu, Y., Zheng, K., Wang, Y., Zhang, W.J., 2014. The green tea extract epigallocatechin-3-gallate inhibits irradiation-induced pulmonary fibrosis in adult rats. *Int. J. Mol. Med.* 34, 92–102.
- You, X.Y., Xue, Q., Fang, Y., Liu, Q., Zhang, C.F., Zhao, C., Zhang, M., Xu, X.H., 2015. Preventive effects of *Ecliptae Herba* extract and its component, ecliptasaponin A, on bleomycin-induced pulmonary fibrosis in mice. *J. Ethnopharmacol.* 175, 172–180.
- Yu, J., Che, J., Liu, L., Yang, F., Zhu, X., Cao, B., 2016. Tetrahydropalmatine attenuates irradiation induced lung injuries in rats. *Life Sci.* 153, 74–81.
- Zhang, G.C., Lin, M., Le, J., Qiu, Z.Y., Zhou, X.M., 2014a. Clinical research of Huqi Huoxue decoction in treating idiopathic pulmonary fibrosis. *China J. Chin. Med.* 29, 1269–1270.
- Zhang, H., Shen, W.S., Gao, C.H., Deng, L.C., Shen, D., 2012. Protective effects of salidroside on epirubicin-induced early left ventricular regional systolic dysfunction in patients with breast cancer. *Drugs R. D.* 12, 101–106.
- Zhang, H., Liu, X., Chen, S., Wu, J., Ye, X., Xu, L., Chen, H., Zhang, D., Tan, R., Wang, Y., 2010. Tectorigenin inhibits the in vitro proliferation and enhances miR-338* expression of pulmonary fibroblasts in rats with idiopathic pulmonary fibrosis. *J. Ethnopharmacol.* 131, 165–173.
- Zhang, H.Q., Yau, Y.F., Szeto, K.Y., Chan, W.T., Wong, J., Li, M., 2007. Therapeutic effect of Chinese medicine formula DSQRL on experimental pulmonary fibrosis. *J. Ethnopharmacol.* 109, 543–546.
- Zhang, H.Q., Yau, Y.F., Wong, M.S., Man, O.Y., He, Y.Y., Chan, N., Li, M., 2008. Chinese medicine formula DSQRL versus glucocorticoids for the treatment of experimental pulmonary fibrosis. *J. Ethnopharmacol.* 116, 318–324.
- Zhang, M., Cao, S.R., Zhang, R., Jin, J.L., Zhu, Y.F., 2014b. The inhibitory effect of salvianolic acid B on TGF- β 1-induced proliferation and differentiation in lung fibroblasts. *Exp. Lung Res.* 40, 172–185.
- Zhang, N.D., Han, T., Huang, B.K., Rahman, K., Jiang, Y.P., Xu, H.T., Qin, L.P., Xin, H.L., Zhang, Q.Y., Li, Y.M., 2016. Traditional Chinese medicine formulas for the treatment of osteoporosis: implication for antiosteoporotic drug discovery. *J. Ethnopharmacol.* 189, 61–80.
- Zhang, Y.Q., Liu, Y.J., Mao, Y.F., Dong, W.W., Zhu, X.Y., Jiang, L., 2015. Resveratrol ameliorates lipopolysaccharide-induced epithelial mesenchymal transition and pulmonary fibrosis through suppression of oxidative stress and transforming growth factor- β 1 signaling. *Clin. Nutr.* 34, 752–760.
- Zhao, H., Xie, P., Li, X., Zhu, W., Sun, X., Sun, X., Chen, X., Xing, L., Yu, J., 2015a. A prospective phase II trial of EGCG in treatment of acute radiation-induced esophagitis for stage III lung cancer. *Radiother. Oncol.* 114, 351–356.
- Zhao, L., Wang, X., Chang, Q., Xu, J., Huang, Y., Guo, Q., Zhang, S., Wang, W., Chen, X., Wang, J., 2010. Neferine, a bisbenzylisoquinoline alkaloid attenuates bleomycin-induced pulmonary fibrosis. *Eur. J. Pharmacol.* 627, 304–312.
- Zhao, P., Zhou, W.C., Li, D.L., Mo, X.T., Xu, L., Li, L.C., Cui, W.H., Gao, J., 2015b. Total glucosides of danggui buxue tang attenuate BLM-induced pulmonary fibrosis via regulating oxidative stress by inhibiting NOX4. *Oxid. Med. Cell. Longev.* 2015, 645814.
- Zhou, W., Cheng, X., Zhang, Y., 2016a. Effect of Liuwei Dihuang decoction, a traditional Chinese medicinal prescription, on the neuroendocrine immunomodulation network. *Pharmacol. Ther.* 162, 170–178.
- Zhou, X.M., Zhang, G.C., Li, J.X., Hou, J., 2007a. Inhibitory effects of Hu-qi-yin on the bleomycin-induced pulmonary fibrosis in rats. *J. Ethnopharmacol.* 111, 255–264.
- Zhou, Y., Zhu, W.P., Cai, X.J., Chen, M., 2016b. Atomized paclitaxel liposome inhalation treatment of bleomycin-induced pulmonary fibrosis in rats. *Genet. Mol. Res.* 15, 1–11.
- Zhou, Y., He, Z., Gao, Y., Zheng, R., Zhang, X., Zhao, L., Tan, M., 2016a. Induced pluripotent stem cells inhibit bleomycin-induced pulmonary fibrosis in mice through suppressing TGF- β 1/Smad-mediated epithelial to mesenchymal transition. *Front. Pharmacol.* 7, 430.
- Zhou, Z.T., Wang, J.W., 2007b. Phase I human tolerability trial of gambogic acid. *Chin. J. New Drugs* 16, 79–83.