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

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Tanshinone IIA (PubChem CID: 164676)
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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; DSQRL, Decoction for Strengthening Qi and Replenishing Lung; ECM, extracellular matrix; EGCG, epigallocatechin-3-gallate; EMT, epithelial-mesenchymal transition; EndoMT, endothelial-mesenchymal transition; EOCR, 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, Houttuynia 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, lipooxygenase; 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-κB, 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, salvianolic 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-β1, transforming growth factor-β1; 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

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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 (Hosseinian 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)-β1, Smads, and phosphorylated Smads (*p*-Smads), are concomitant with the ability of epithelial cells to adopt mesenchymal phenotypes (Kolosova 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

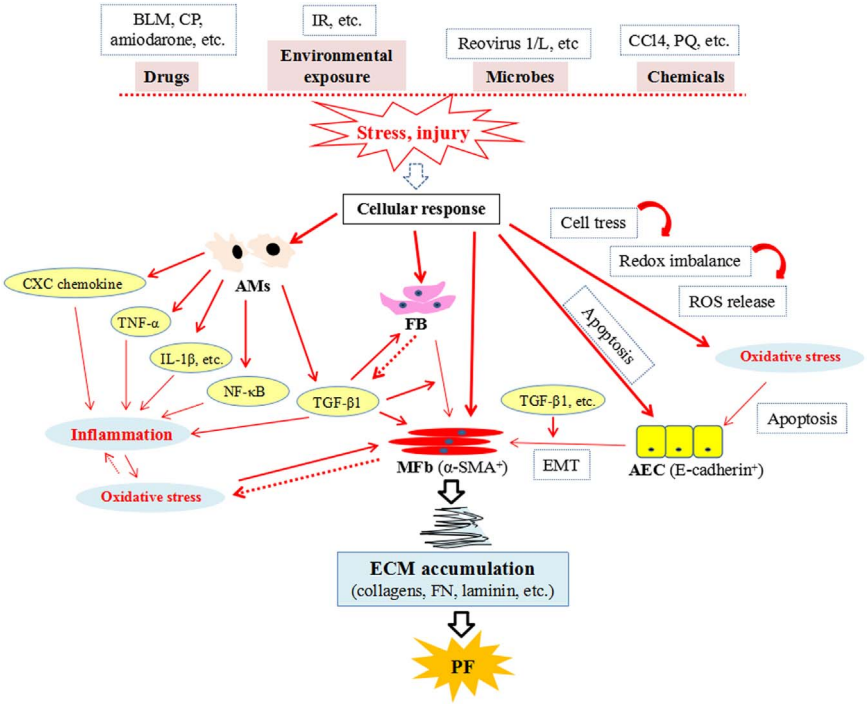

Fig. 1. The pathological mechanisms of pulmonary fibrosis. A series of factors (drugs, IR or else) trigger the continuous development of pulmonary fibrosis by inducing cell stress *via* superabundant inflammation, macrophages activation, abnormal FB proliferation, FB to MFb transformation, EMT and oxidative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