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Review

The efficacy of plant extract and bioactive compounds approaches in the treatment of pulmonary fibrosis: A systematic review

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ABSTRACT

Pulmonary fibrosis (PF) is a lethal, chronic and progressive respiratory disease leading to interstitial lung damage and serious breathing problems. The pathogenic mechanism involves activation, migration, proliferation and differentiation of fibroblasts into myofibroblats inducing extracellular matrix accumulation that destroy lung parenchyma. Available antifibrotic treatment options are limited to Pirfenidone and Nintedanib that prevent deterioration without an improvement of this disease. The use of plant extracts and natural bioactive compounds for the treatment of PF has been known for more than thirty years in China. Nowadays, phytotherapy has gained a considerable attention in the treatment of PF both *in vivo* and *in vitro* using bleomycin (BLM)-induced lung inflammation, oxidative stress and pulmonary fibrosis in rats. In this review, we aimed to focus on the protective effects and the mechanisms of action of several plant extracts described by various research works for the treatment of PF.

Contents

Abbreviations: AMPK, AMP-activated protein kinase; BLM, bleomycin; BW, body weight; CCl4, Carbon Tetrachloride; CTGF, Connective Tissue Growth Factor; ERK, Extracellular signal-Regulated Kinase; FGF, Fibroblast Growth Factor; GST, gluthatione S transferase; GPx, Glutathioneperoxidase; GSH-Px, Glutathione peroxidase; IFN-$_\gamma$, interferon alpha; IL, interleukin; JAK-STAT, The Janus kinase/signal transducers and activators of transcription; Keap1/Nrf2, Keap 1/Nuclear factor (erythroid-derived 2)-like 2; MAPK, Mitogen-activated protein kinases; MDA, malondialdehyde; MMP, metalloproteinases; NF-$_\kappa$B, nuclear factor-kappa B; PDGF, Platelet-Derived Growth Factor; ROS, Reactive oxygen species; SOD, superoxide dismutase; TIMP, Tissue inhibitors of metalloproteinases; TGF-β, Transforming Growth Factor-beta; TNF-α, Tumor Necrosis Factor – α; VASH, Vasohibin; VEGF, Vascular endothelial growth factor; α-SMA, α -smooth muscle actin.

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1. Introduction

Pulmonary fibrosis (FP) is a lung disease characterized by the formation of fibroblastic foci in the pulmonary parenchyma. The pathological mechanisms at the origin of fibrotic process and architectural disorganization are a product of fibroblasts dysfunction with an excessive proliferation affecting the connective tissue. This tissue becomes thick and rigid, which alter lung distensibility and O_2/CO_2 diffusion. These disturbances of gas exchange lead inevitably to a respiratory insufficiency.

Three main anomalies are implicated in the physiopathology of PF: *(i)* alveolar epithelial lesions induced by genetic and/or environmental factors, *(ii)* vascular disorders with abundant neo-vascularization of non-fibrotic tissue and *(iii)* oxidative stress, in which ROS formation play a key role (Fig. 1). It is currently admitted that chronic inflammation is not the only cause of PF installation, as there is also fibroblasts proliferation and their differentiation into myofibroblasts. This process lead to aberrant scarring and extracellular matrix accumulation at the origin of collagen deposition (Fig. 2) [1].

Myofibroblasts ensure the maintenance of the connective tissue, but also its pathological transformation in case of exaggerated proliferation. Due to their contractility, these cells can modulate the thickness of the interstitial tissue, since in the absence of lung injury, the pulmonary epithelium have a very low mitotic activity. In case of fibrosis, the increase in the thickness of the alveolar-capillary membrane stiffens the lung and alters gas exchange.

This chronic disease presents two major difficulties for the physicians: a diagnostic one, because the confirmation of the latter necessitates a panoply of complementary examinations, and a therapeutic one, due to the fact that there is no effective and innocuous treatment till now. Thus, the prognosis of PF remains unfavorable and 30% of patients with PF die within 5 years after the installation of the disease [1].

1.1. Current therapeutic strategies

Many therapies are currently in the testing phase by targeting mainly growth factors and cytokines, which play a direct role in fibroblasts proliferation, activation, differentiation or in their inadequate survival. Researchers are testing the direct effect of therapeutic molecules on growth factors activities, their receptors or mediators involved in signal transduction.

Other therapies have been developed to indirectly limit fibroblasts activation, by inhibiting the profibrotic action of fibrocytes or the recruitment of monocytes and macrophages. Others have been interested in endothelial cells. These cells are important to limit vascular leakage and to spill plasma proteins into the alveolar space, in order to promote temporary extracellular matrix deposition [2].

In October 2014, Pirfenidone and Nintedanib were approved by the US Food and Drug Administration (FDA) for the treatment of PF. Pirfenidone (5-methyl-1-phenyl-2- [1H] pyridone) has antioxidant, anti-inflammatory and antifibrotic effects and showed a reduction in worsening of this disease but no benefit on acute exacerbation [3]. Nintedanib, an intracellular inhibitor of tyrosine kinases, was reported to reduce PF progression, by exerting an anti-angiogenic, anti-inflammatory and anti-fibrotic activities. The preventative administration of nintedanib can also decrease acute exacerbation [4]. These two drugs decreases PF related mortality but their cost remains expensive.

Lung transplantation remains the only alternative treatment that can significantly improve life expectancy of patient by reducing the risk of death to 75% [5]. Therefore, research on PF

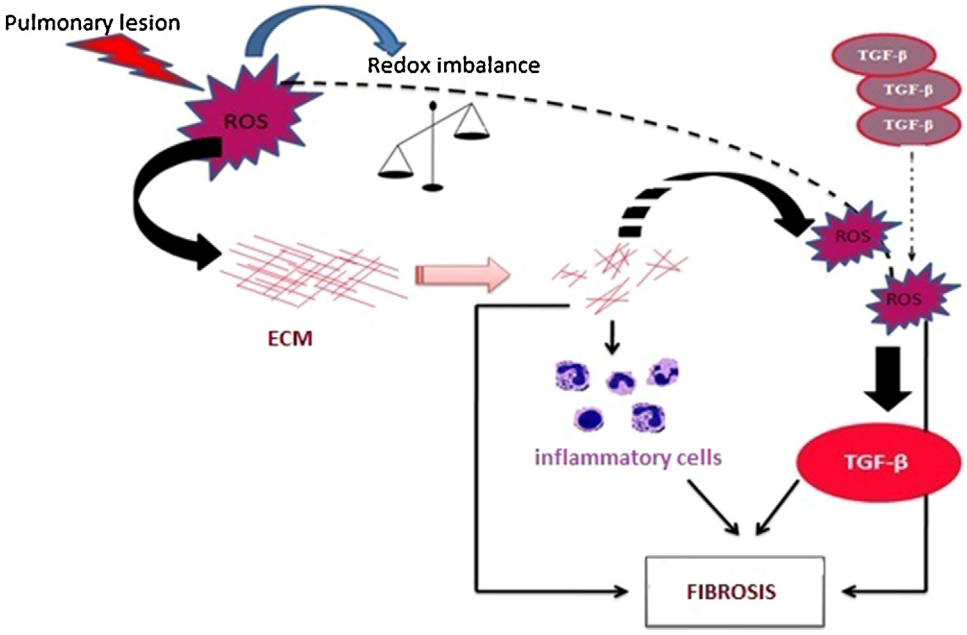

Fig. 1. Involvement of ROS in the pathogenesis of pulmonary fibrosis. Pulmonary lesions induce a redox imbalance and ROS production in lung cells, which can lead to ECM degradation, the recruitment of inflammatory cells and an increase of ROS production. ROS can also activate cytokines such as TGF-β which improve the fibrosing process.