

• Review

Effects of herbal extracts and compounds and pharmacological agents on pulmonary fibrosis in animal models: a review

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ABSTRACT

Pulmonary fibrosis, a chronic inflammatory disease that occurs mainly in older adults, is a serious health threat with few effective treatment options. The etiological aspects of pulmonary fibrosis remain unknown, though some factors such as cigarette smoking, viral infections, surfactant protein polymorphisms, and chronic or high doses use of certain drugs are considered to be risk factors for the progression of pulmonary fibrosis. No standard treatments have been introduced in clinic yet. Although glucocorticoids and antioxidant drugs have been administered, the severe and broad-spectrum adverse effects of glucocorticoids limit their use. Efforts to identify novel therapeutic agents with improved safety profiles are therefore ongoing. In this review, the authors have described the effects of herbal extracts and compounds and certain pharmacological agents on pulmonary fibrosis in animal models. These effects indicate that herbs are a promising source of compounds that can play pivotal roles in the treatment of lung fibrosis.

Keywords: pulmonary fibrosis; herbal medicine; pharmacological agents; bleomycin; paraquat

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1 Introduction

Pulmonary fibrosis is a progressive and potentially lethal inflammatory disease of the lung, characterized by excessive deposition of extracellular matrix components in the interstitium, which ultimately leads to fibrotic changes in the alveoli and respiratory failure.^[1,2] Despite differences in diagnostic criteria, the incidence of pulmonary fibrosis is very high in both Europe and USA.^[3] Further, a recent

study indicated that the current incidence of pulmonary fibrosis in the USA among people aged 65 years and older is higher than that reported 10 years ago.^[4] According to the latest statistics, though pulmonary fibrosis has a low incidence rate (13–42 cases per 100 000 persons), the incidence is dramatically high among older adults.^[5] The risk factors of pulmonary fibrosis include aging, smoking, certain infections caused by herpes viruses and bacteria, exposure to herbicides such as paraquat and drugs such as

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bleomycin and amiodarone (Figure 1).^[6,7] Additionally, an aberrant wound-healing response may lead to massive lung injury and fibrosis.^[8] Severe cases of pulmonary fibrosis involve extensive damage to all parts of the lungs and severe dyspnea.^[1,2,9-13] Although the etiology of pulmonary fibrosis is not well understood, inflammation and oxidative stress are known to play central roles in its initiation and progression. Studies at the cellular level reveal that chronic inflammation and modulation of fibrogenesis are the key events that induce fibrosis.^[14] It has also been reported that fibrotic responses are initiated in the fibroblast foci, which are areas that contain actively proliferating myofibroblasts and fibroblasts.^[15-17] In addition, an increase in myofibroblast contractility has been observed in rats with paraquat-induced lung fibrosis.^[18]

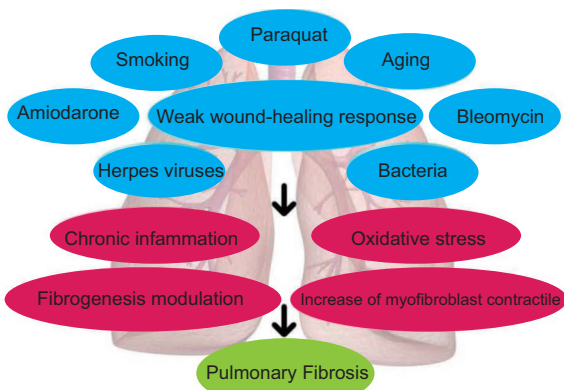


Figure 1 Different factors related to pulmonary fibrosis induction

Animal models have played a pivotal role in the search for antifibrotic agents for treating pulmonary fibrosis, with several models being used to examine pulmonary pathobiology.^[19] Several agents have been employed to induce lung fibrosis in animal models. Bleomycin, which induces transforming growth factor- β (TGF- β) expression^[20] and extensive immunologic reactions,^[21] and paraquat, which increases oxidative stress and free radical formation,^[22] are two major chemical inducers of lung fibrosis in animals. In the paraquat-induced pulmonary fibrosis model, a single oral dose of paraquat (40 mg/kg) was administered in rats. The treatment groups received experimental compound 5 d prior to administration of paraquat and treatment was continued for 2 weeks.^[23] In bleomycin-induced pulmonary fibrosis model, bleomycin solution (7.5 IU/kg) was administered intra-tracheally to induce pulmonary fibrosis. In treatment groups, rats received experimental compound 7 d before bleomycin instillation, and the treatment continued for up to 3 weeks.^[24]

Although certain anti-inflammatory drugs (prednisolone) and cytotoxic drugs (cyclophosphamide) are currently

being used for treating pulmonary fibrosis, their clinical usage is limited by the many severe side effects associated with their chronic use.^[19] New drugs such as nintedanib have been developed and approved for treatment of pulmonary fibrosis. However, some unwanted effects such as acute nausea, diarrhea and changes in liver enzyme activity may lead to discontinuation of these drugs in patients.^[25] Pirfenidone is another new drug which is specifically employed in pulmonary fibrosis patients. Using pirfenidone may show gastrointestinal, neurological and dermatological adverse effects.^[26] Deleterious side effects of conventional and chemical drugs are motivating factors for many to seek herbal treatment for pulmonary fibrosis, which may be associated with fewer adverse effects. This paper is a review of the effects of extracts and active compounds obtained from herbs as well as certain pharmacological agents on pulmonary fibrosis in animal models.

2 Effects of herbal extracts on pulmonary fibrosis in animal models

Various herbal extracts that have been shown to possess antifibrotic activity are listed in Table 1.

Reactive oxygen species (ROS) is believed to play an important role in paraquat-induced pulmonary fibrosis. The administration of *Berberis vulgaris* fruit extract to rats with paraquat-induced pulmonary fibrosis normalized the oxidative stress, thus reducing the induced toxicity.^[27] Similarly, *Passiflora edulis* fruit peel extract has been reported to dramatically reduce inflammation and collagen accumulation in lung tissues and normalize the activity of enzymes such as superoxide dismutase and myeloperoxidase in mice with bleomycin-induced pulmonary fibrosis.^[28] The antifibrotic activity of the total extract of Yupingfeng formula (a Chinese herbal medicine composes of *Astragali Radix*, *Atractylodis Macrocephalae Rhizoma* and *Saposhnikoviae Radix*) against bleomycin-induced pulmonary fibrosis in rats has been demonstrated via evaluation of hydroxyproline content, histopathological parameters and the expression of high-mobility group box 1, TGF- β 1, collagen type I (Col-I), and α -smooth muscle actin (α -SMA) proteins.^[29] In our study, we observed that treatment with pomegranate seed extract prevented the histopathological changes associated with bleomycin-induced pulmonary fibrosis in male Sprague-Dawley rats.^[13] The effect of *Glycyrrhiza glabra* (Licorice), which has anti-asthmatic and immunomodulatory effects on bleomycin-induced pulmonary fibrosis in mice, has also been investigated. The results indicated that the aqueous extract of *G. glabra* reduced the expression of α -SMA, TGF- β 1, interleukin-1 β (IL-1 β), and tumor necrosis factor- α

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