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REVIEW

Herbal Compounds in the Treatment of Pulmonary Silicosis

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Summary

Herbal compounds including those already well-established in traditional Chinese medicine have been increasingly tested in the treatment of various diseases. Recent studies have shown that herbal compounds can be of benefit also for pulmonary silicosis as they can diminish changes associated with silica-induced inflammation, fibrosis, and oxidative stress. Due to a lack of effective therapeutic strategies, development of novel approaches which may be introduced particularly in the early stage of the disease, is urgently needed. This review summarizes positive effects of several alternative plant-based drugs in the models of experimental silicosis with a potential for subsequent clinical investigation and use in future.

Key words

Pulmonary silicosis • Inflammation • Fibrosis • Anti-inflammatory treatment • Herbal treatment

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Introduction

Herbal compounds have ben already well-established in traditional Chinese medicine for treatment of various diseases. Several of plant-based medicines have been successfully used as an adjunctive treatment in many respiratory disorders including inflammatory lung diseases, bronchial asthma, chronic obstructive pulmonary disease, cough or COVID-19 (Wagner *et al.* 2015, Santana *et al.* 2016, Shergis *et al.* 2016, Ang *et al.* 2020, Yang and Yang 2021).

Recent studies have shown that herbal compounds can be of benefit also for pulmonary silicosis (Li *et al.* 2017a, Peng *et al.* 2017, Liu *et al.* 2019, Zhu *et al.* 2020, Li *et al.* 2021a). Pulmonary silicosis is a serious fibrotizing disease caused by prolonged and/or long-term inhalation of silica particles. The changes accompanied with silica inhalation, such as accumulation of lymphocytes and alveolar macrophages in the interstitium, thickening of the pulmonary interstitium mass, formation of hyalinized fibrotic nodules, and deposition of collagen fibres, are strongly associated with silica-induced inflammation and oxidative stress. Because of complex pathophysiology of the disease, persistence of silica particles in the lung, and perpetuation of pro-inflammatory and pro-fibrotic cascades, development of novel approaches targeting inflammation and fibrosis particularly in the early stages of the disease is urgently needed. This article provides a short review of pathophysiology of pulmonary silicosis as a rationale for recommended therapy and summarizes the positive effects of several alternative plant-based drugs in the models of experimental silicosis with a potential for subsequent clinical investigation and use in future.

Pulmonary silicosis

Intensive and/or long-term exposure to inhaled silica results into a complex and still not fully understood activation of several pathomechanisms (Hamilton *et al.* 2008, Harijith *et al.* 2014, Sayan and Mossman 2016). For better understanding the rationale of the treatment, a short overview of the pathomechanisms and their

interactions is provided in the subsection below, while more details may be found in our recent article (Adamcakova and Mokra 2021).

Inhaled silica crystals are extremely toxic to the lung tissue. Due to their piezoelectric properties, they directly trigger a generation of reactive oxygen species (ROS) (Hamilton *et al.* 2008). Silica particles are rapidly recognized by receptors on the surface of alveolar macrophages, or airway epithelial cells, and subsequently engulfed by these cells (Øvrevik *et al.* 2006, Hamilton *et al.* 2008). However, the internalized silica cannot be broken by lysosomal enzymes what leads to damage of lysosomal membrane integrity and silica freed from destroyed macrophages can be internalized by other macrophages generating a vicious cycle of silica toxicity to alveolar macrophages (Hamilton *et al.* 2008). Released lysosomal enzymes including protease cathepsin B, ROS overproduction, activation of the surface receptors with activation of the related pro-inflammatory pathways, e.g. nuclear factor (NF)-κB and mitogen-activated protein kinase (MAPK), K^+ efflux, extracellular adenosine triphosphate (ATP) etc. subsequently stimulate an activation of nucleotide-binding and oligomerization domain-like receptor (NLR)P3 inflammasome, a special intracellular receptor complex (Tschopp and Schroder 2010, Sayan and Mossman 2016). Activation of NLRP3 inflammasome triggers an activation of caspase-1 which induces a pyroptosis, a highly pro-inflammatory type of cell death, which is linked with a release of interleukin (IL)-1α, IL-1β, IL-18, high mobility group box 1 protein (HMGB1), ROS *etc.* (Bergsbaken *et al.* 2009). These mediators trigger an expression of other pro-inflammatory cytokines including tumor necrosis factor (TNF)α which increase the influx of neutrophils into the lung and damage the epithelial cells. The mentioned bioactive substances, particularly IL-1β, enhance a recruitment of fibroblasts and a production of pro-fibrotic transforming growth factor (TGF)-β. TGF-β induces activation, proliferation, and transdifferentiation of epithelial cells and fibroblasts into myofibroblasts generating components of extracellular matrix, e.g. collagen. High concentrations of pro-fibrotic substances and recruitment of collagen- and fibronectin-producing cells predispose to formation of silicotic nodules, scaring the lung tissue and reduction of areas providing a gas exchange (dos Santos *et al.* 2012, Pardali *et al.* 2017).

Excessive concentrations of produced ROS cause mitochondrial dysfunction, forcing alveolar macrophages to undergo a mitochondrial apoptosis. However, in this form of cell death, alveolar macrophages release cell organelles and high amounts of bioactive substances and ROS further injuring the lung tissue. To prevent a potential injury, autophagy as a special form of cell elimination sequesters dysfunctional and potentially toxic macromolecules and injured organelles into double-membrane autophagosomes (Kim and Lee 2014) and damaged mitochondria may be eliminated by mitochondria-selective autophagy (or mitophagy) (Palikaras *et al.* 2018). Reducing production of ROS, autophagy and mitophagy prevent the excessive secretion of pro-inflammatory factors and eventual progression of fibrosis induced by silica.

Treatment of pulmonary silicosis

Because of no causal pharmacological treatment of silicosis, patients are treated only symptomatically using bronchodilators and antitusic and mucolytic agents (Barnes *et al.* 2019). Important is also prevention of the additional exposures to silica and curing the respiratory infections (Cullinan and Reid 2013). In several trials, a whole lung lavage was used in acute silicoproteinosis to decrease a presence of dust particles and inflammatory cells in the bronchoalveolar lavage fluid (BALF) (Zhang *et al.* 2012) but this approach had no effect on long-term outcome or mortality or even increased a risk of complications (Stafford *et al.* 2013). As a last resort after exhaustion of other therapeutic options, lung transplantation may be indicated. However, long-term survival after lung transplantation has a poor prognosis (Lopes-Pacheco *et al.* 2016).

Several novel experimental approaches are based on suppression of activation of inflammasome, e.g. by reduction of oxidative stress by antioxidants, restoring the function of autophagy-lysosomal system, or by blocking pro-inflammatory cytokines or pro-fibrotic factors (Harijith *et al.* 2014, Lee *et al.* 2014, Song *et al.* 2014, Sugimoto *et al.* 2019, Zahid *et al.* 2019, Caseley *et al.* 2020). Favorable results have been also published for treatment with microRNA (Das *et al.* 2014, Xu *et al.* 2019, Qi *et al.* 2020), mesenchymal stem cells (Liu *et al.* 2015a, Chen *et al.* 2018, Li *et al.* 2018) or extracellular vesicles from mesenchymal stem cells (Choi *et al.* 2014, Phinney *et al.* 2015, Bandeira *et al.* 2018). Some improvement for lung fibrosis including silicosis can be also found for agents increasing cyclic adenosine monophosphate (cAMP) or guanosine monophosphate (cGMP), e.g. inhibitors of phosphodiesterases (Rabolli

et al. 2011, Abdelaziz *et al.* 2016, Fehrholz *et al.* 2017, Sisson *et al.* 2018, Kolb *et al.* 2018, Wu *et al.* 2020), or for corticosteroids (Barbarin *et al.* 2005, Trentin *et al.* 2015, Ferreira *et al.* 2020).

Treatment with herbal compounds

In addition to the previously mentioned approaches, there is an increasing number of experimental studies demonstrating a wide potential of herbal drugs in the treatment of lung silicosis. Some of these plant-based compounds can influence one or even several of the pathomechanisms of silicosis and thereby they can mitigate the silica-induced inflammation and/or fibrosis.

In the following part of this article, effects of the most promising phytomedicines are discussed. Dosages and modes of delivery are listed in Table 1, natural sources and chemical structure of the compounds are provided in Figure 1.

Table 1. Dosages and modes of delivery of herbal treatments in experimental models of silicosis.

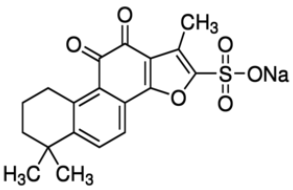
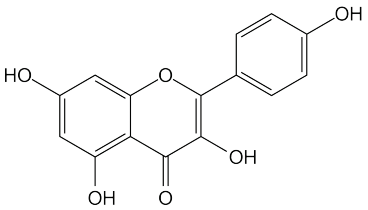
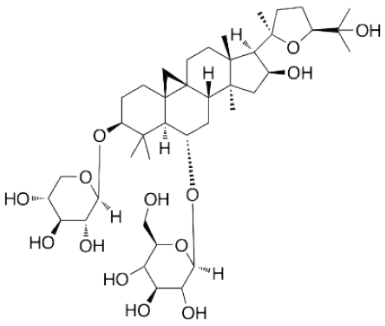
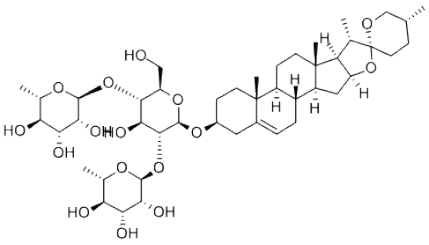
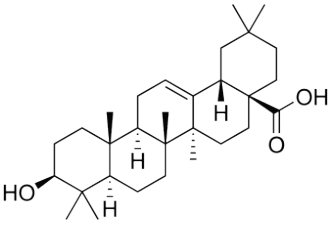
Compound	Model of silicosis	Mode of delivery	Daily dose	References
Sodium tanshinone IIA sulfonate	Rat	i.p.	25 mg/kg	Zhu *et al.* 2020
Kaempferol	Mouse	i.p.	150 mg/kg	Liu *et al.* 2019
Astragaloside IV	Rat	i.p.	20 mg/kg	Li *et al.* 2019
Dioscin	Mouse	p.o.	80, 40, or 20 mg	Du *et al.* 2019, Li *et al.* 2017a
Oleanolic acid	Rat	i.g.	60 mg/kg	Peng *et al.* 2017
Hesperetin	Rat	i.g.	100, 200, or 400 mg/kg	Li *et al.* 2021
Emodin	Mouse	i.p.	20 mg/kg	Yang *et al.* 2016

Abbreviations: i.p.: intraperitoneally, p.o.: orally, i.g.: intragastrically.

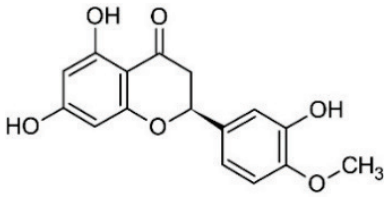
Sodium tanshinone IIA sulfonate

Sodium tanshinone IIA sulfonate (STS) is a hydrosoluble extract of *Salvia miltiorrhiza* which is used in traditional Chinese medicine for the treatment of coronary heart disease. Moreover, STS has shown its potent antioxidant, anti-inflammatory, and anti-apoptotic actions in various diseases through regulating various transcription factors including NF-κB and through influencing Ca^{2+}, K^{+} and Cl^{-} ion channels (Zhou *et al.* 2019, Zhu *et al.* 2020).

In a rat model of silicosis, intraperitoneal injection of STS significantly reduced collagen deposition in the lung and reduced ROS as demonstrated by a decrease in production of malondialdehyde (MDA), a marker of lipid peroxidation in oxidative stress. Authors presume that the anti-fibrotic effects of STS may be related to upregulation of nuclear factor erythroid 2-related factor 2 (Nrf2) expression and nuclear translocation and the subsequent increase in transcription of thioredoxin and its reductase (Zhu *et al.* 2020). Antioxidant and anti-fibrotic effects of STS were previously demonstrated in bleomycin-induced pulmonary fibrosis where STS reduced a production of lipid peroxides and hydroxyproline (Wang *et al.* 1994) as well as in *in vitro* model of lipopolysaccharide-induced pulmonary fibrosis where STS downregulated the protein expressions of IL-1β and TNFα, and inhibited TGF-β1-induced cell proliferation and overexpression of α-smooth muscle actin (SMA) and collagen-1 (Jiang *et al.* 2020). Promising results have been also demonstrated in other types of the lung injury. For instance, in a rat model of seawater-aspiration and in isolated alveolar type II cells, STS attenuated a generation of pulmonary edema enhancing the activity of K^{+}-ATPase, Na^{+} and extracellular signal-regulated kinases (ERK)1/2 (Xie *et al.* 2011). In a rabbit model of endotoxemia, STS pretreatment reduced injury to the lung, heart, and liver (Ma *et al.* 2018).

Compound	Source	Chemical structure
Sodium tanshinone IIA sulfonate		
Kaempferol		
Astragaloside IV		
Dioscin		
Oleanolic acid		

Hesperetin



Emodin

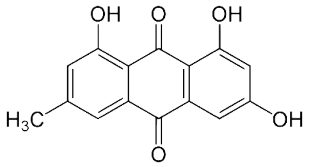


Fig. 1. Herbal compounds used in the experimental treatment of pulmonary silicosis.

Kaempferol

Kaempferol (Kae) is a flavonoid widely present in many plants, fruits and vegetable (Amaral-Machado *et al.* 2020). Kae exerts wide anti-inflammatory, anti-oxidative and anti-fibrotic effects including inhibition of TLR4 receptor, NF-κB and MAPK pathways, suppression of the release of IL-6, IL-1β, IL-18 and TNFα, attenuation of oxidative stress *via* activation of Nrf2-ARE signaling pathway *etc.* (Alam *et al.* 2020, Amaral-Machado *et al.* 2020).

In a murine model of silicosis, intraperitoneally administrated Kae modulated silica-induced autophagy and significantly inhibited pulmonary inflammation at day 7 what was demonstrated by lower expressions of pro-inflammatory cytokines, and inhibited silica-induced pulmonary fibrosis at day 28 what was demonstrated by suppressed activation of matrix metalloproteinase-2 and smaller silicotic nodules (Liu *et al.* 2019).

Astragaloside IV

Astragaloside IV (ASV) is one of the most active compounds isolated from root of an inedible herb *Astragalus membranaceus.* This herb is widely used in traditional Chinese medicine to treat several fibrotic diseases including systemic sclerosis and liver fibrosis (Zhang *et al.* 2020), however, it might be also effective in silicosis and other types of lung fibrosis. For instance, Li *et al.* (2019) found that intraperitoneally injected ASV once a day to rats with silicosis can reduce the expression of markers of fibrosis, i.e. α-SMA as a marker of activation of myofibroblasts, and collagen I and collagen III as markers of abundant production of extracellular matrix. The therapeutic action of ASV may be partially mediated by suppression of TGF-β1/Smad3 signaling pathway as a continuous phosphorylation of Smad3 is a major factor in causing fibrosis (Li *et al.* 2021a). Similarly in bleomycin-induced lung fibrosis in rats, ASV downregulated the levels of HMGB1 in serum and lung tissue and inhibited the bleomycin-upregulated expression of α-SMA and other markers of synthesis of lung extracellular matrix (collagen III, laminin, hyaluronic acid, hydroxyproline) (Li *et al.* 2017b).

ASV treatment may also prevent the fibrosis downregulating TGF-β1/PI3K/Akt pathway as it was demonstrated in a rat model of bleomycin-induced pulmonary fibrosis (Qian *et al.* 2018). Presumably due to suppression of TGF-β1/PI3K/Akt pathway, intragastric ASV given daily for 14 days starting at day 15 of induction of fibrosis modulated a TGF-β1-dependent epithelial-mesenchymal transition (EMT) (Qian *et al.* 2018). Potent antioxidant and anti-inflammatory effects of ASV may be also related to inhibition of NF-κB expression (Zhang and Frei 2015) and agonism with glucocorticoid receptors (Zhang *et al.* 2020). In bleomycin-induced lung fibrosis model in rats, intraperitoneal ASV given daily for 28 days attenuated markers of oxidative stress and inflammation what was confirmed by decreased counts of inflammatory cells and concentrations of TNFα, IL-1β and IL-6 in BALF (Yu *et al.* 2016).

In a recent *in vitro* study, ASV prevented invasion and EMT of TGF-β-induced cells, delaying a progress of pulmonary fibrosis. In addition, ASV downregulated expression of NLRP3 inflammasome (Hou *et al.* 2021). This finding is in accordance with other studies where ASV prevented an activation of NLRP3 inflammasome (Wan *et al.* 2018, Qu *et al.* 2019).

Dioscin

Dioscin is a widely occurring steroidal saponin present in a variety of vegetables and herbs, particularly in the species of *Dioscoreaceae*, *Liliacae* and *Solanacae* (Yang *et al.* 2019). Because of potent anti-inflammatory, immunoregulation, hypolipidemic, anti-viral, anti-fungal, and anti-allergic effects, dioscin has wide medicinal and pharmaceutical applications in various disorders including tissue fibrosis (Tao *et al.* 2018). Likely *via* inhibiting the TLR4/MyD88/NF-κB signaling pathway, dioscin decreased pro-inflammatory cytokines TNFα, IL-1β and IL-6, declined pro-fibrotic factors TGF-β1, α-SMA, collagen I and fibronectin, inhibited EMT, and thereby attenuated a peritoneal fibrosis (Shao *et al.* 2019) or alleviated alcoholic liver fibrosis (Liu *et al.* 2015b). However, promising results have been also demonstrated in the pulmonary silicosis. In murine models of silicosis, daily oral administration of dioscin exerted anti-inflammatory and anti-fibrotic effects through alleviating an apoptosis of alveolar macrophages and promoting an autophagy, a special protective form of the cell elimination (Du *et al.* 2019). Dioscin-stimulated autophagy mitigated a silica-induced release of mitochondrial ROS, mitochondrial dysfunction, and apoptosis of alveolar macrophages what resulted in reduced generation of pro-inflammatory factors, and decreased inflammatory lung infiltration and collagen deposition (Du *et al.* 2019).

Oral administration of dioscin to mice with silicosis mitigated a recruitment of fibrocytes, a direct source of fibroblasts, prevented a fibroblast activation, and inhibited TGF-β/Smad3 signaling, leading together to decreased collagen deposition and delayed fibrosis (Li *et al.* 2017a). In addition, dioscin protected the epithelial cells from silica-induced injury, and reduced macrophage and lymphocyte lung infiltration and secretion (Li *et al.* 2017a).

As recently published, enhancing alveolar macrophage autophagy and mitophagy may protect the lung not only from silica-induced injury (Tan *et al.* 2021) but may be valuable also in other forms of the lung fibrosis (Zhao *et al.* 2020).

Oleanolic acid

Oleanolic acid (OA) is a plant-derived pentacyclic terpenoid which exists naturally in vegetable oil, food and certain medicinal herbs either as a free acid or as an aglycone of triterpenoid saponins (Pollier and Goossens 2012). OA exhibits numerous pharmacological properties, including hepatoprotective, anti-oxidative, anti-inflammatory and anti-cancer effects (Pollier and Goossens 2012). Anti-oxidant and hepatoprotective effects are mediated *via* activation of PI3K/Akt, JNK, and ERK pathways leading to an increase in nuclear accumulation of Nrf2 (Liu *et al.* 2008, Wang *et al.* 2010). Anti-inflammatory and anti-cancer effects are likely mediated by targeting NF-κB pathway (Laszczyk 2009). Thus, OA and its derivatives possess a wide range of potential applications in disorders associated with inflammation and oxidative stress, including renal and liver fibrosis (Pollier and Goossens 2012, Chung *et al.* 2014) and lung silicosis (Peng *et al.* 2017).

Intragastric daily administration of OA to silicotic rats significantly attenuated an extent of silica-induced fibrosis including content of collagen types I and III and reduced oxidative stress what was expressed by a decrease in MDA content and increased activities of anti-oxidant systems (superoxide dismutase and glutathione peroxidase) in the lung. Furthermore, OA decreased the levels of TNFα and TGF-β1. These results suggest that the protective effects of OA may be related to both the anti-oxidant activity and the ability to decrease the expression of cytokines and to suppress a synthesis of collagen by modulating the Akt/NF-κB pathway (Peng *et al.* 2017).

Hesperetin

Hesperetin (HSP) is a natural flavonoid present e.g. in citrus fruits that exhibits wide anti-inflammatory, anti-oxidative, anti-bacterial, and anti-cancer effects (Iranshahi *et al.* 2015, Parhiz *et al.* 2015). The anti-inflammatory action of HSP is likely mediated *via* increasing the expression of peroxisome proliferator-activated receptor (PPAR)-γ and inhibiting the activation of NF-κB pathway (Ma *et al.* 2015). In an *in vitro* study, pretreatment of fibroblasts with HSP protected the cells from peroxynitrite-mediated cytotoxicity by intracellular scavenging of ROS and peroxynitrite and modulation of ERK signaling (Hirata *et al.* 2005, Pollard *et al.* 2006). Reduction of oxidative stress by HSP is partially

attributable to stimulation of anti-oxidant systems, as well (Choi *et al.* 2008).

In rats exposed to silica, HSP reduced an extent of alveolitis and pulmonary fibrosis, declined levels of MDA, increased activity of anti-oxidant enzymes and total antioxidant capacity, inhibited the synthesis and secretion of TGF-β1, decreased levels of pro-inflammatory cytokines IL-1β, IL-4, and TNFα, and elevated levels of anti-inflammatory factors IFN-γ and IL-10 (Li *et al.* 2021b).

Emodin

Emodin may be extracted from several plants, including *Reynoutria japonica Houtt*, and *Rheum officinale Baill*. Emodin has been used in traditional medicines in Eastern and Southern Asia because of anti-inflammatory, anti-cancer and anti-fibrotic effects (Cui *et al.* 2020). Anti-inflammatory effects of emodin were shown in animal models of ovalbumin-induced airway inflammation and hyperreactivity (Wang *et al.* 2015) and in models of lipopolysaccharide-induced lung, liver and systemic inflammation (Xiao *et al.* 2014, Jia *et al.* 2014). The mentioned effects may be mediated by inactivation of NF-κB pathway (Xiao *et al.* 2014) and/or by attenuation of activation of NLRP3 inflammasome (Han *et al.* 2015).

Potent anti-fibrotic effects of emodin were demonstrated in rats with pancreatic fibrosis where emodin suppressed expressions of TGF-β1 and collagen and decreased serum levels of hyaluronic acid and laminin, markers of fibrosis (Wang *et al.* 2007). Similarly in rats with liver fibrosis, emodin suppressed TGF-β1 signaling and EMT (Liu *et al.* 2018). Very promising results for emodin were also found in animal models of bleomycin-induced lung fibrosis (Chen *et al.* 2009, Guan *et al.* 2016). In bleomycin-instilled mice, emodin reduced biochemical markers (hydroxyproline content and myeloperoxidase activity) and histopathological markers of lung fibrosis, and decreased TGF-β, IL-4, and IL-13 in BALF. In addition, emodin decreased fibroblast proliferation and collagen production in a cell culture in adose-dependent manner (Chen *et al.* 2009). In more recent study, emodin enhanced pulmonary function and improved survival of bleomycin-injured animals, reduced TNFα, IL-6, TGF-β1 and heat shock protein, alleviated lung edema, decreased collagen deposition and expression of α-SMA, suppressed lung infiltration of myofibroblasts, macrophages, and lymphocytes and inhibited TGF-β1-induced Smad2/3 and STAT3 activation (Guan *et al.* 2016).

Emodin was beneficial in animal models of lung silicosis, as well. In a murine model of silica-induced lung fibrosis, emodin improved pulmonary function and reduced deposition of collagen I and α-SMA in the lung. The anti-fibrotic effects of emodin were given into relation with emodin-induced increase of sirtuin (Sirt)1 which downregulates TGF-β1/Smad fibrotic signaling (Yang *et al.* 2016). In silica-exposed mice, emodin reduced the degree of alveolitis and fibrosis in the lung, inhibited a phosphorylation of Smad3 and NF-κB and reduced the levels of TGF-β1, α-SMA, collagen-I, TNFα and IL-1β in the lung tissue. In addition, emodin inhibited apoptosis by downregulating the pro-apoptotic protein Bax and upregulating the anti-apoptotic protein Bcl-2. Furthermore, emodin reduced the expressions of markers of fibrosis, apoptosis and inflammation in *in vitro* cultured human macrophages and alveolar epithelial cells (Pang *et al.* 2021). The above-mentioned results indicate that emodin can regulate the inflammatory response, EMT and fibrotic process at multiple levels inhibiting the TGF-β1/Smad3 signaling pathway and the NF-κB signaling pathway.

Conclusions

Because of complicated pathophysiology, the treatment of pulmonary silicosis is extremely difficult. However, recent studies performed on the experimental models of silicosis have shown that there are several therapeutic approaches which might be of benefit. Among them, positive effects have been found for plant-based compounds which may influence various signaling pathways participating in the development of silica-induced lung fibrosis. With respect to favorable results of herbal medicines in the experimental models of silica-induced lung injury, positive and eventual adverse effects of these treatments should be studied in clinical trials in future to objectively verify a therapeutic potential of these substances.

Conflict of Interest

There is no conflict of interest.

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