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Review

# Effects of plant extracts and bioactive compounds on attenuation of bleomycin-induced pulmonary fibrosis

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ABSTRACT

*Introduction:* Bleomycin (BLM) is a chemotherapeutic agent that is used in the management of some human cancers such as lymphomas and squamous cell carcinomas. The major limitation of BLM therapy is pulmonary toxicity. Combining medicinal herbs and chemotherapy drugs are proposed to attenuate this side effect of BLM.
*Methods:* We conducted a search of some databases such as PubMed for articles and reviews published between 1998 and 2018, with different keywords including “bleomycin”, “pulmonary fibrosis”, “plant extract”, “bioactive compound”, “herbal preparation”.
*Results:* Studies revealed that these natural products have several mechanisms of action to ameliorate pulmonary fibrosis such as inhibitory effects against the elevation of inflammatory markers such as NF-κB and preventing an increase in fibrotic markers like MMP-9 and HYP. Among the plant extracts that were evaluated, *Chrysanthemum indicum* enhanced the anti-cancer activity of BLM and showed a synergistic effect with BLM besides, substantial potential in improving BLM induced pulmonary fibrosis.
*Conclusion:* In conclusion, the present review demonstrates that the herbs and their active ingredients are a promising source of compounds that can play pivotal roles in the alternative adjuvant chemotherapy in reducing the pulmonary fibrosis of BLM.

## 1. Introduction

Bleomycin (BLM), is a key component of chemotherapy commonly employed in the treatment of Hodgkin lymphoma and testicular germ-cell tumors, the most highly curable cancers [1]. The mechanism of action and cytotoxic activity of BLM is exerted through inhibition of DNA and protein synthesis [2]. The toxic effects of BLM are generally attributed to formation of free radicals and organ specificity is driven by catalysing hydrolase which is poorly expressed in lung and skin tissue, rendering these organs vulnerable to toxicity [3]. Clinically, treatment with BLM is very limited due to the development of dose-dependent pneumonitis that can progress to interstitial pulmonary fibrosis [4]. BLM induced pulmonary fibrosis may occur in up to 10 percent of the patients receiving the drug [5]. Patient’s symptoms and signs with BLM lung toxicity are dyspnea, fever, cough, sputum, thoracic pain, tachypnea, cyanosis, pleuritic pain and pleural rubbing. A number of risk factors have been identified in several clinical studies including cumulative dose above 400 IU, tobacco smoking and patients older than 70 years which have an increased susceptibility to develop BLM-induced lung injury [6].

Cytokines and free radicals are key effectors of BLM-induced lung injury. BLM stimulates alveolar macrophages to secrete inflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, IL-18, IL-22 and IL-17a and endothelial cells to secrete IL-6. Fibroblasts are activated early in BLM-induced lung injury through stimulation of fibronectin which is produced by damaged endothelial cells or stimulation by cytokines such as TNF, platelet derived growth factor (PDGF) and transforming growth factor β (TGF_β). Continued exposure of lung

*Abbreviations:* AMPK, AMP-activated protein kinase; BLM, bleomycin; COX 2, cycloxigenase-2; EMT, epithelial mesenchymal transition; GPx, glutathione peroxidase; GST, gluthatione S transferase; HYP, hydroxyproline; IFN-α, interferon alpha; IL, interleukin; JAK-STAT, the Janus kinase/signal transducers and activators of transcription; LOX2, lysyl oxidase 2; LPO, lipid peroxide; MAPK, mitogen-activated protein kinases; MDA, malondialdehyde; MMP, metalloproteinases; MPO, myeloperoxidase; NF-κB, nuclear factor-kappa B; Nrf 2, nuclear factor (erythroid-derived 2)-like 2; PDGF, platelet-derived growth factor; ROS, reactive oxygen species; SOD, superoxide dismutase; TGF-b, transforming growth factor-beta; TIMP, tissue inhibitors of metalloproteinases; TNF-α, tumor necrosis factor – α; α-SMA, α -smooth muscle actin

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**Table 1**
Summary of findings on plant extracts effects against pulmonary fibrosis.

| Plant | Type of extract | Tests | Dose (mg/kg) Animal/Route | Active ingredients | References |
|---|---|---|---|---|---|
| *Ginkgo biloba* | | TNF-α<br>Lung collagen content<br>LPO | 100 mg/kg<br>Rat /Oral | Flavonoids<br>Ginkgolide B<br>Ginkgolide C | [3] |
| *Vitis vinifera* | Aqueous | TGF-β1<br>MMP-9<br>Cytokines (IL-1, IL-6)<br>Profibroticmarkers (COL1A1, FN1) | 100 mg/kg<br>Mice/Oral | Proanthocyanidins | [8] |
| *Trigonellafoenum graceum* | Hydroalcoholic | Nrf2<br>Fibrotic molecules (TNF-α, IL-1, IL-6, IL-8, HO-1) | 200 mg/kg<br>Rat/Oral | Glycosides (vicenin-1, trigoneoside) | [14] |
| *Rosmarinus offivinalis* | Ethanolic | GST<br>Catalase<br>MDA | 75 mg/kg<br>Rat/Intraperitoneal | Polyphenol | [17] |
| *Chrysanthemum indicum* | | IL-6<br>TNF-α<br>TGF-β1<br>MPO<br>MDA | 240 and 360 and 480 mg/kg<br>Mice/Oral | Glycosides<br>Flavonoids | [19] |
| *Paenial lactiflora* | Aqueous | HYP<br>α-SMA<br>Type1collagen | 50 mg/kg<br>Mice/Oral | Paeoniflorin | [22] |
| Rhodiola rosea | Ethanolic | GSH<br>MMP-9<br>TGF-β | 125 and 250 and 500 mg/kg<br>Rat/Oral | Flavonoids<br>Polyphenols | [25] |
| *Houttuynia cordata* | Aqueous | SOD<br>MDA<br>INF-γ<br>TNF-α | 1 g/kg<br>Rat/Oral | Aristolactam<br>Indoles | [28] |
| *Eclipta prostrate* | Ethanolic | HYP<br>TGF-β1<br>MMP-9 | 2.5 and 1.25 and 0.625 mg/kg<br>Mice/Oral | Saponins<br>Triterpenes | [31] |
| *Radix astragalus* | | -SMAα<br>TGF-β1<br>Jagged1/Notch1expression | 8 mg/kg<br>Rat/ Intraperitoneal | Astragaloside | [33] |
| *Passiflora edulis* | Methanolic | Neutrophil accumulation | 100 mg/kg | Anthocyanins | [36] |
| *Citrus reticulata* | Aqueous | MPO activity | Mice/Oral | Flavonoids | [38] |
| *Nigella sativa* | | SOD | 5 and 10 and 20 mg/kg | Flavonoids | [40] |
| *Juglans regia* | | HYP | Rat/Oral | Alkaloids | [41] |
| *Silybum marianum* | | TGF-β1<br>FS<br>Urinary secretion<br>TGF-β1<br>HYP<br>LPO<br>NO<br>MPO<br>NF-κB<br>MPO<br>MDA<br>LPO<br>GSH<br>Catalase, GST<br>IL-10, IL-12 | 1mg/kg<br>Rat/Oral<br>100 mg/kg<br>Rat /Oral<br>50 and 100 mg/kg<br>Mice/ Intraperitoneal | Anthocyanins<br>Thymoquinone Ellagic acid<br>Flavonoid | [47] |

to BLM can lead to increasing collagen synthesis and deposition of various matrix proteins including collagen, elastin, and proteoglycan. Moreover, BLM-activated alveolar macrophages stimulate the synthesis of hyaluronan, a connective tissue molecule that is seen in fibrotic lungs [7]. Interventions designed to limit the consequences of the inflammatory response. Due to few patients respond to the anti-inflammatory therapies and the prognosis remains poor [2], there is an urgent need for developing new drugs for the treatment of pulmonary fibrosis (PF) (Tables 1–4).

In this review, we conducted a search of some databases such as PubMed, Scopus and Science direct for articles and reviews published between 1998 and 2018, with different keywords including “bleomycin”, “pulmonary fibrosis”, “plant extract”, “bioactive compound”, “herbal preparation” and the connectors AND or OR (Fig. 1).

The results are categorized into three groups including plant extracts, herbal preparations and bioactive compounds.

## 2. Results

### 2.1. Plant extracts

#### 2.1.1. Ginkgo biloba

*Ginkgo biloba,* a member of the Ginkgoaceae family is native to China. It is assumed that the antioxidant effect of *Ginkgo biloba* extract is based on flavonoids, ginkgolides B, C and bilobalide [8]. Bilobalide has shown anti-inflammatory properties and neuroprotection in preclinical models of stroke and Alzheimer’s disease [9].

The effects of *Ginkgo biloba* extract on BLM induced lung fibrosis in rats were investigated. The extract has been shown to regulate the ionic balance in the damaged cells and exert a specific and potent platelet-activating factor antagonistic activity. Furthermore, this study showed that administration of this extract could exhibit an inhibitory effect against the elevation of serum TNF-α and lipid peroxide (LPO) level