

Standardized Herbal PM014 Formula Ameliorates Pulmonary Fibrosis in COVID-19 Patients by Inhibiting the TGF- β 1 Signaling Pathway

Maryam Allahverdi-Khani¹ , Luis Ulloa² , Majid Motaghinejad^{3*} , Mahsa Salehirad⁴ 

1. Clinical Research Development Center, Najafabad Branch, Islamic Azad University, Najafabad, Iran
2. Dept. of Anesthesiology, Center for Perioperative Organ Protection, Duke University, Durham, NC, USA
3. Chronic Respiratory Disease Research Center (CRDRC), National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
4. Cognitive and Neuroscience Research Center (CNRC), Amir-almomenin Hospital, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

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ABSTRACT

A number of studies have previously provided evidence on the Anti-inflammatory properties of plant-derived compounds that can prevent lung injury. In this study, we attempted to analyze the therapeutic effects of PM 014 on inflammation and pulmonary fibrosis in COVID-19 as well as describing the treatment of one of the most challenging problems related to the coronavirus-19 (COVID-19). We believe that having a close look at all angles of the proposed mechanism goes beyond the physiological consequences of a way to design new strategies for providing an appropriate treatment.

Keywords: COVID-19, Anti-inflammatory, Plant-derived, TGF- β , Pulmonary fibrosis

Corresponding Information:

Majid Motaghinejad,

Chronic Respiratory Disease Research Center (CRDRC), National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

E-Mail:

dr.motaghinejad6@gmail.com



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Introduction

Viruses causing severe respiratory infections mostly lead to seasonal epidemics, which affect a large number of patients worldwide. Moreover, these have the risk of producing global pandemics with dramatic medical and economic burdens. These infections may require patient's hospitalization with a significant mortality rate, especially in those patients with underlying immune disorders, including adolescents or the elderly. These viruses have already caused various pandemics with high mortality rates all around the world, depending on the type of the virus [1]. For instance, the 1918 influenza pandemic caused nearly 50 million deaths worldwide and the current COVID-19 pandemic has already led to over half a million deaths during the first 5 months [1, 2]. The main target of these viral diseases is the respiratory system, especially the upper respiratory tract, and the main cause of death among the infected patients is pulmonary

immunopathology [2, 3]. Viral infection triggers immune responses, including cytotoxic mechanisms, which have the potential of destroying the infected cells and clearing the virus [2, 3]. However, this inflammatory response can also affect normal tissue and then cause organ injury beyond the need to clear the virus only. An overzealous production of inflammatory cytokines or the so-called 'cytokine storm' with causing acute lung injury and respiratory failure, can become more dangerous than the infection itself [1, 3, 4].

Numerous studies have previously shown that plant-derived compounds have anti-inflammatory properties preventing lung injury [5, 6]. Among them, Panax ginseng and Salvia miltiorrhiza have been found with the potential to be used for the treatment of lung diseases. Moreover, in Korea, the standardized herbal Chung-Sang-Bo-Ha-Tang (CSBHT) PM014 formula has been

traditionally used to treat chronic pulmonary disease, and recent studies concur in its potential of reducing lung inflammation [5, 6].

Considering the roles of inflammation and pulmonary fibrosis in COVID-19, we hypothesized that the herbal PM014 formula might be represented as a therapeutic strategy for the treatment of lung injury in COVID-19.

Hypothesis

Recent studies on COVID-19 cases have shown that severe acute respiratory syndrome–coronavirus 2 (SARS-CoV2) is a lethal and uncontrollable pathogen resulting in an inflammatory ‘cytokine storm’, thereby affecting the upper respiratory tract. Currently, there is no effective treatment proposed for COVID-19, which has caused over half a million deaths during the first five months of the pandemic. Herein, we discussed a novel potential therapeutic approach for the treatment of lung injury in COVID-19.

Of note, both inflammatory cytokines and chemokines can cause idiopathic pulmonary fibrosis (IPF), which might result in fibroblast activation, myoblast proliferation, and extracellular matrix deposition. In this regard, one of the most prominent mediators is transforming growth factor (TGF)- β 1, which induces epithelial-mesenchymal transmission (EMT) in alveolar cells and also triggers the differentiation of fibroblasts into myofibroblasts. Moreover, TGF β 1, which is mainly induced in acute and chronic pulmonary diseases, contributes into the recruitment of monocytes into the lung [7]. Additionally, TGF- β 1 can activate several signaling cascades, subsequently aggravating some pathological changes in IPF.

Recent studies have reported that PM014 herbal formula by targeting EMT can protect body against pulmonary inflammation and fibrosis. PM014 can also inhibit TGF- β 1 signaling, thereby preventing TGF- β 1-induced EMT in alveolar epithelial cells A549 [8]. Given that coronavirus infections mostly affect the lungs and then lead to the development of the severe acute

respiratory syndrome, PM014 may be considered as a potential therapeutic approach for COVID-19.

Conclusion

In this study, we examined the potential mechanism of PM014 in the treatment of COVID-19 patients with lung injury and respiratory syndrome. Multiple studies in this field have shown the potential of PM014 in controlling lung injury during pulmonary inflammation in different types of diseases, including experimental models of radiation-induced pulmonary inflammation [6, 8]. Considering the anti-inflammatory potential of PM014 in lung-related diseases, we hypothesized that PM014 may protect lungs against idiopathic pulmonary fibrosis among COVID-19 patients. To test this hypothesis, we analyzed the potential of PM014 in controlling EMT in human alveolar basal epithelial A549 cells treated with bleomycin.

It was observed that PM014 regulates the production of anti-inflammatory cytokines in both acute and chronic lung inflammations as well as the response to inflammation during the onset of inflammatory mediators. As well, the respective increase and decrease in epithelial and mesenchymal markers revealed the protective potential of PM014 against IPF, respectively [9]. Additionally, histopathological data implied that PM014 could inhibit goblet cell hyperplasia and improve structural changes of the lungs [8]. At the molecular level, these results showed that PM014 could significantly inhibit the mesenchymal morphology phenotype of EMT in A549 cells stimulated with TGF- β 1 [9]. Furthermore, our review revealed the potential of PM014 in blunting TGF- β 1 signaling and pulmonary fibrosis, which supports the idea that PM014 can be considered as a good and suitable candidate for the treatment of COVID-19 patients with the severe respiratory syndrome (Figure-1).

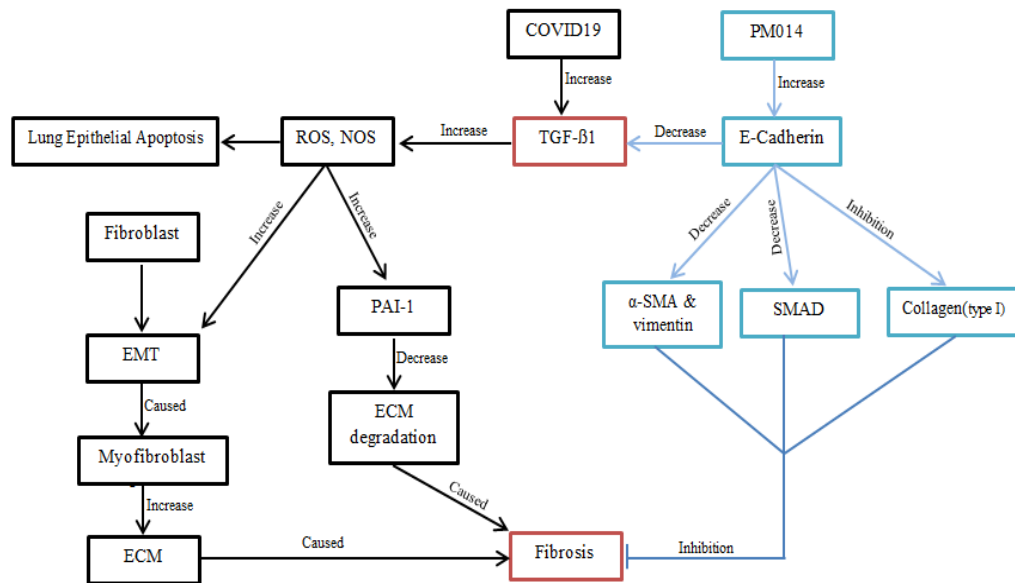


Figure 1. A standardized herbal extract PM014 by suppressing the TGF- β 1 pathway, ameliorates COVID-19-induced pulmonary fibrosis. COVID-19 can cause the increased production of TGF- β 1, which consequently leads to the activation of both ROS and NOS and causes lung epithelial apoptosis as well as the activation of EMT. Subsequently, these processes converts fibroblast to Myofibroblast and increase the production of ECM, leading to lung fibrosis. In addition, COVID-19 induction increases in TGF- β 1, and ROS and NOS lead to the increased PAI-1. Accordingly, this causes the decreased ECM degradation and one of the consequences of this phenomenon is lung fibrosis. On the other hand, PM014, as a standardized herbal extract, can possibly cause the activation of E-cadherin protein, resulting in the inactivation of TGF- β 1 pathway and a reduction in formation lung fibrosis after COVID-19 infection. Besides, PM014 could inhibit three main proteins, including α -SMA/Vimentin, SMAD, and Collagen (type-1), which are involved in lung epithelia cell. As a result of this inhibition, these proteins directly inhibit the occurrences of lung fibrosis after COVID-19 infection. TGF- β 1: transforming growth factor (TGF)- β 1; EMT: epithelial-mesenchymal transmission; ROS: reactive Oxygen Species; NOS: Nitrogen Oxygen Species; ECM: extracellular matrix; and PAI-1: profibrogenic mediator inducing-1.

Acknowledgments

None.

Conflict of Interest

None.

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