Guo Y, et al., HSOA J Altern Complement Integr Med 2025, 11: 652
DOI: 10.24966/ACIM-7562/100652

HSOA Journal of
Alternative, Complementary & Integrative Medicine

Research Article

Natural Products Protect Lung Diseases by Targeting the Hippo Signaling Pathway

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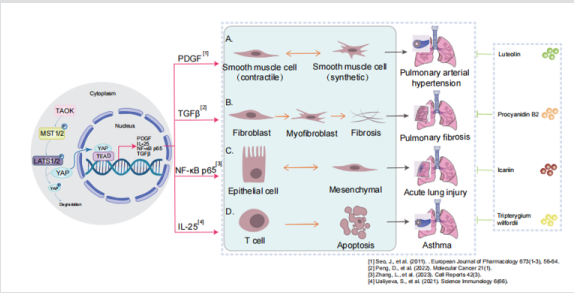
Abstract

Respiratory illness and diseases are common problems worldwide. Natural products have become a source of drug discovery for respiratory diseases. The Hippo signaling pathway is a highly conserved evolutionary pathway. This article summarizes the protective role of natural products in lung diseases such as pulmonary arterial asthma, acute lung injury, pulmonary arterial hypertension and idiopathic pulmonary fibrosis and explains how they exert protective effects through the Hippo signaling pathway. In addition, natural products targeting the Hippo signaling pathway may be promising drug candidates for lung diseases. Consequently, further research is required to focus on the mechanism of natural products and drug targets in Hippo signaling pathway, especially in lung diseases.



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Citation: Guo Y, Jiao Z, Xu Y, Wang C, Jia T, et al. (2025) Natural Products Protect Lung Diseases by Targeting the Hippo Signaling Pathway. HSOA J Altern Complement Integr Med 11: 652.

Received: November 09, 2025; **Accepted:** November 20, 2025; **Published:** November 27, 2025

Introduction

Plants or herbs containing natural compounds have been used for centuries in traditional medicine and have made significant contributions to the pharmacological treatment of various diseases [1]. Natural products have emerged as a valuable source of novel bioactive lead compounds in drug discovery, characterized by multi-target effects, stable therapeutic efficacy, low side effects and no drug dependence [2].

Over the years, natural products have been the subject of extensive investigation for their potential in the treatment of lung diseases, with a particular focus on their impact on different classical signaling pathways [3]. EA (Ellagic Acid) has been shown to significantly suppress fibroblast activation and ECM (Extracellular Matrix) production through inhibition of the Wnt/Akt and Erk signaling pathways [4]. Tripterine and procyanidin B2 improve the occurrence and the development of lung diseases through the Hippo signaling pathway [5-7].

The Hippo signaling pathway has been reported to play an important role in lung development and alveolar differentiation [8]. Beyond impaired alveolar differentiation, lung diseases involve multiple pathological processes. Chronic inflammation drives tissue damage through cytokine release and immune cell infiltration [9]. Fibrosis, characterized by excessive extracellular matrix deposition (e.g., collagen), disrupts lung architecture in conditions like idiopathic pulmonary fibrosis, YAZ/TAP induces myofibroblast differentiation and excessive extracellular matrix deposition, leading to tissue scarring. Vascular remodeling—including endothelial dysfunction and pulmonary hypertension—compromises gas exchange [10]. Airway remodeling features goblet cell hyperplasia, smooth muscle hypertrophy, and submucosal gland enlargement in obstructive diseases such as asthma and COPD, the Hippo signaling pathway function is associated with defective alveolar epithelial regeneration and airspace enlargement [11]. Additionally, oxidative stress, protease-antiprotease imbalances, and epithelial-mesenchymal transition contribute to progressive tissue injury and functional decline [12]. We will summarize the role and mechanism of natural products in Pulmonary Hypertension (PAH), asthma and Acute Lung Injury (ALI) through the Hippo signaling pathway.

Hippo Signaling Pathway

The Hippo signaling pathway, first identified in Drosophila melanogaster, is one of the earliest developmentally conserved pathways [13,14]. It gets its name from the key member of the pathway, Hippo protein kinase, which has been studied for 20 years [15].

The pathway consists of a series of conserved kinases (MST1/2 and LATS1/2 , as examples) [16] that regulate cell proliferation, apoptosis, stem cell self-renewal [17,18], which are involved in a variety of biological functions, such as tissue development, maintenance of tissue homeostasis, and regenerative repair [19]. The imbalance in the Hippo pathway leads a wide range of diseases, such as heart disease, liver disease, lung disease, and immune dysfunction [20,21].

Hippo signaling pathway is a kinase cascade in which MST1/2 kinase /Salvador (SAV1) complex phosphorylate and activate LATS1/2 kinase [22-24]. The transcriptional coactivators YAP and TAZ—key downstream effectors—are phosphorylated by LATS1/2 [25,26]. Upon dephosphorylation, YAP/TAZ complex is translocated to the nucleus, where it interacts with TEAD1-4 and other transcription factors to induce the expression of genes that promote cell proliferation and inhibit apoptosis [27]. Moreover, the Hippo signaling pathway plays a role in cell-contact inhibition [28].

The Hippo pathway is orchestrated through a tightly controlled kinase cascade. MST1/2 and LATS1/2 kinases are activated by upstream regulators including scaffold proteins (Merlin, KIBRA, RASSF) and the LIM-domain protein Ajuba, which facilitate signal integration [29,30] . Phosphatases dynamically modulate MST1/2 and YAP/TAZ phosphorylation status [31,32], and ubiquitination controls LATS1/2 and YAP/TAZ protein stability [32]. Cytoskeletal tension further fine-tunes LATS1/2 activity [33]. Concurrently, cytoplasmic retention complexes containing 14-3-3, α-catenin, AMOT, and ZO-2 sequester YAP/TAZ at cell junctions, preventing nuclear accumulation. [34].

Upon pathway inactivation, dephosphorylated YAP/TAZ translocate to the nucleus [35] where they form transcriptional complexes with TEAD1-4. These complexes drive expression of proliferative (CTGF, Connective Tissue Growth Factor), survival (AXL, Receptor Tyrosine Kinase), and differentiation-related genes [36]. Notably, the TEAD-induced Ajuba protein creates a negative feedback loop by directly inhibiting MST1/2 and LATS1/2 kinases [37], establishing a self-regulating circuit that maintains pathway homeostasis. This dual-layered regulation ensures precise spatial-temporal control of YAP/TAZ activity in response to mechanical and biochemical cues.

Briefly, the Hippo signaling pathway negatively regulates the transcriptional activity of its downstream effector YAP, which plays an important role in maintaining homeostasis of cell proliferation and apoptosis by limiting overgrowth in most tissues [38].

Natural Products and Lung Diseases

The effects of natural products in Asthma

Asthma, caused by a combination of genetic and environmental factors, is a chronic inflammatory disease of the respiratory tract that affects approximately 300 million people worldwide and is responsible for at least 250,000 deaths annually [39,40]. The global median incidence rate of asthma is 402 people per 100000 people, and the incidence rate of children under 10 years old is growing [41].

Asthma is a heterogeneous respiratory disease characterized by reversible bronchial obstruction [42]. The airway epithelium is the first structural barrier against inhaled environmental damage and plays a key role in the development of allergic airway inflammation [43]. Current asthma medications (e.g., bronchodilators, corticosteroids, theophyllines) alleviate symptoms but exhibit side effects due to narrow therapeutic windows, while inhaled corticosteroids are more effective, yet none provide a cure, leading to reduced quality of life [44,45].

Significant upregulation of the YAP protein in bronchial airway tissues was observed in an OVA-induced chronic asthma mouse model. Furthermore, the study proved that tripterine (Tripterygium wilfordii) treatment attenuated LPS-induced (Lipopolysaccharide-induced) airway epithelial barrier dysfunction by inhibiting the protein level of YAP/TAZ in the Hippo pathway, which in turn delayed the development of chronic asthma [6].

The effects of natural products in ALI

ALI is a significant cause of severe respiratory failure, which is caused by infection, severe shock, or pulmonary trauma [46]. ALI is a life-threatening disease characterized by immune cell infiltration and diffuse alveolar injury, ultimately leading to pulmonary edema, hypoxemia, and organ failure, with high morbidity and mortality [47]. Meanwhile, the excessive lung inflammation and apoptosis of alveolar epithelial cells (AECs) play key roles in the pathogenesis of ALI [48].

The key clinical bottleneck in ALI pharmacotherapy is that current anti-infectives (e.g., cephalosporins) only manage symptoms but cannot prevent disease progression, ultimately requiring surgical intervention [49]. An understanding of the mechanism of alveolar epithelial cell regeneration ability provides a theoretical basis for the treatment of ALI. It has been reported that the Hippo signaling pathway is involved in the repair process of ALI by improving the proliferation and differentiation of lung epithelial cells [50]. YAP has been reported to enhance the self-renewal of alveolar epithelial type II cells (AECIIs) and promote their differentiation into type I alveolar epithelial cells (AECIs) in lung injury. [8,51]. Furthermore, YAP-mediated proliferation and differentiation of AECIIs regulate AECIs in response to mechanical tension [8]. During alveolar regeneration, mechanical forces enhance AECII responsiveness, triggering nuclear YAP accumulation. YAP promotes AECII proliferation and differentiation into AECIs while driving pulmonary endothelial repair through angiogenic factors [52]. MST1/2 deletion and YAP target proteins further regulate epithelial cell dynamics. These findings implicate the Hippo pathway in ALI repair by modulating both epithelial regeneration and vascular remodeling [8].

Procyanidin B2 (PB2) has been demonstrated to elevate phosphorylation by inhibiting the expression of LATS1/2 and YAP in the Hippo signaling pathway at both the mRNA and protein levels [7]. And PB2 reduces the levels of inflammatory cells in the serum and lung tissue of sepsis induced ALI mice, alleviating LPS induced ALI in the peritoneum [7]. Therefore, PB2 has anti-inflammatory and lung-protective effects on sepsis-induced ALI and is a potential therapeutic drug.

The effects of natural products in PAH

PAH is a chronic, progressive, and irreversible disease with a high mortality rate, characterized by a sustained increase in pulmonary vascular pressure and pulmonary vascular resistance, culminating in right heart failure and sudden death [53,54]. According to most European data, the estimated annual incidence rate of PAH is 5.8 adults per million, and the prevalence rate is 47.6 to 54.7 adults per million [55]. In recent years, notable advancements have been made in the diagnosis and treatment of PAH. However, it remains difficult to reverse the outcome and reduce the high mortality rate of PAH. The pathogenesis of PAH includes abnormal contraction of the pulmonary arteries, endothelial dysfunction, vascular remodeling and in situ thrombosis [56]. Vascular remodeling is mainly caused by abnormal proliferation and migration of pulmonary artery smooth muscle cells (PASMCs) [57].

The mainstay pharmacotherapies for pulmonary arterial hypertension (PAH) - including prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors - primarily provide symptomatic relief and hemodynamic improvement without altering disease progression [58]. Therefore, there is a need for new target

studies and new potential drug candidates. Hippo signaling pathway plays an important role in vascular remodeling [59,60]. Inactivation of LATS1 promotes YAP nuclear translocation, driving PASMC proliferation and vascular remodeling [61]. Consistently, smooth muscle-specific MST1/2 knockout in hypoxic PAH mice activates YAP via impaired phosphorylation, subsequently upregulating Akt-mTORC1 signaling [62].

Studies have shown that luteolin exerts protection by inhibiting YAP, which in turn inhibits the activation of the downstream PI3K/AKT pathway in part [63]. luteolin extract is a potential candidate drug in PAH.

The effects of natural products in IPF

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, irreversible, and often fatal lung disease with unknown etiology and limited treatment options [64]. It is characterized by changes in the composition and homogeneity of peripheral lung cells, leading to an excessive accumulation of ECM and destruction of alveolar structure, resulting in respiratory failure and death [65]. According to the epidemiological survey of IPF, the global incidence rate of IPF ranges from 0.09 per 10000 people to 1.30 per 10000 people, and increases year by year [66].

The commonly used drugs for IPF are nintedanib and pirfenidone, which only delay its progression with certain side effects [67]. Nintedanib can cause diarrhea and other gastrointestinal symptoms, while pirfenidone is closely related to skin adverse reactions, especially photosensitivity, and has a certain probability of causing gastrointestinal intolerance [68]. Nintedanib-induced diarrhea typically occurs during early treatment, with most patients experiencing symptoms within 1–2 weeks of initiation [69,70]. Therefore, it is necessary to pay attention to new promising candidate drugs.

Recent studies have shown that YAP/TAZ in the Hippo signaling pathway is a key coordinator of fibroblasts activation with increased synthesis of ECM, and expression of pro-fibrotic factors [71]. Overexpression of YAP has been shown to promote the proliferation and migration of fibroblasts, induce collagen production, and inhibit epithelial cell differentiation, thereby exacerbating the disease progression of idiopathic pulmonary fibrosis [72]. In addition, the inhibition of YAP signaling blocks TGF-β-induced fibroblast to myofibroblast transformation and ECM deposition, whereas activation of YAP is sufficient to promote fibroblast differentiation and ECM deposition [73].

Recent research reports that Icariin (ICA) attenuates BLM-induced pulmonary fibrosis in rat model by inhibiting inflammatory response, profibrotic activity, and expression of YAP and collagen [64]. The treatment of ShaShen MaiDong (Adenophora stricta Miq) resulted in inhibition of YAP/TAZ and phosphorylation of YAP. ShaShen MaiDong suppresses IPF and and alleviates BLM induced pulmonary fibrosis in mouse by simultaneously regulating the TGF - β/Smad3, AKT/MAPK, and YAP/TAZ pathways, indicating that they are potential natural compounds for treating IPF [74]. In summary, ICA and SMT can treat bleomycin induced pulmonary fibrosis by inhibiting the Hippo signaling pathway, which may be promising candidate drugs.

Conclusion and Prospect

Beyond the roles in PAH, asthma, ALI, and IPF summarized above, the Hippo pathway also contributes to the pathogenesis of chronic obstructive pulmonary disease (COPD) and pneumonia.

COPD affects nearly 400 million people and is already the third leading cause of death worldwide , which is characterized by persistent respiratory symptoms and progressive airflow obstruction documented by spirometry [75]. The occurrence and development of COPD is associated with an abnormal inflammatory response of the lungs to toxic particles or air pollution [76,77]. Studies have shown that E-calmodulin activates Hippo signaling pathway in lung epithelial cells [78]. Exposure to air pollution has been demonstrated to result in a reduction in E-calmodulin expression and YAP phosphorylation in A549 cell proliferation and A549 cell senescence, which may subsequently trigger emphysema in patients with COPD [78].

Pneumonia is an infection of the lungs caused by bacteria, viruses, or other microorganisms. The mortality rate of pneumonia accounts for 30% of all respiratory system deaths [79]. The alveolar epithelium plays a key role in protecting the lungs from inhaled infectious agents. Surface-active protein C-expressing (SPC-expressing) AECIIs undergo proliferation and differentiation after infection, which is reported to be associated with increased expression of YAP and TAZ in nuclear [8]. Deficiency of YAP in AECIIs leads to a sustained accumulation of inflammatory cells in the lungs in bacterial pneumonia [80]. In YAP/TAZ-deficient mice, the signaling pathways regulating the resolution of lung inflammation are significantly dysregulated, the lungs exhibit prolonged inflammatory response [8]. Given the critical role of YAP/TAZ in lung disease pathogenesis, targeting this pathway may represent a promising therapeutic strategy.

Oleanolic acid, a small molecule natural product, has been reported to inhibit ECM degeneration in osteoarthritis by regulating the Hippo/YAP and Wnt/β-catenin pathways [81]. Liquiritigenin (LQ) has been shown to be antioxidant, anti-inflammatory, antitumor, and antidiabetic activities. LQ treatment induced YAP phosphorylation and inhibits YAP/TAZ activation, which ultimately blocks HSC activation and the development of liver fibrosis [82]. Cordycepin administration upregulates the expression of MST1 and LATS1, thereby inhibiting the expression of YAP1, and thus exerts anti-cancer effects [83]. Therefore, evaluating oleanolic acid and Liquiritigenin (LQ)—natural compounds targeting the Hippo/YAP pathway—has become a warranted strategy for future research into lung disease treatment.

Natural products have been studied for a long period of time and the relevant drugs are widely used in clinical practice.This review underscores the targeting of the Hippo signaling pathway as an emerging therapeutic strategy for lung diseases and provides a comprehensive overview of promising natural product-derived drug candidates to modulate this pivotal pathway.

Acknowledgement

This work was supported in part by Noncommunicable Chronic Diseases-National Science and Technology Major Project (2024ZD0528200 to J.Z); and the National Natural Science Foundation of China (82370068 and 81771513 to J.Z.).

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