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The Therapeutic Effects of Oridonin in Pulmonary Diseases

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1. Abstract

Oridonin (Ori) is a natural diterpenoid compound that can be isolated from Isodon rubescens. It has been reported that Ori has anti-inflammatory, anti-tumor, anti-oxidation and anti-apoptosis effects. Ori has been shown to play a vital role in pulmonary diseases, degenerative diseases, stroke and malignant tumors. In this paper we summarize the structure, pharmacological action, related molecular pathways and the roles of Ori in lung diseases, in order to provide a new idea for the development of drugs for lung diseases.

2. Introduction

Respiratory disease is a common and frequently occurring disease. The main lesions in the trachea, bronchus, lungs and chest. Cough and chest pain were more common in mild cases, while dyspnea and even respiratory failure were more common in severe cases. Due to factors such as air pollution, smoking and industrial development, the incidence of respiratory diseases such as lung cancer, bronchial asthma, chronic obstructive pulmonary disease has increased significantly in recent years. This shows that respiratory diseases are still very harmful to people's health, and the prevention and therapy are significant [1-3]. Traditional Chinese medicine (TCM) has a history of thousands of years and has always occupied a vital position [4]. With the emergence of SARS-COV-2, the treatment of lung diseases by TCM has received renewed attention [5]. Studies have showed that monomer is more meaningful than decoction. Because the monomer component is single and the therapeutic effect is relatively stable [6]. Many TCM monomers have been found to play an important role in the treatment of lung diseases, including Pterostilbene, Resveratrol, Dapnetin, and Ori [7-9]. Ori, a natural diterpenoid compound, exerts anti-inflammatory and anti-tumor effects. In recent years, an increasing number of studies focus on the relationship between Ori and acute/chronic lung diseases. This article mainly discusses the therapeutic effect of Ori in diverse pulmonary diseases, so as to provide theoretical basis and future perspectives for TCM treatment.

3. Structure and Pharmacological Action of Ori

Ori is the main component of Isodon rubescens. The molecular formula is C20H28O6 and the relative molecular mass is 364.44 (Figure 1). Colorless prismatic crystal, bitter taste, insoluble in water, slightly soluble in ether, methanol, ethanol and other organic solvents. It has good stability, good absorption, distribution, metabolism, excretion and safety in the body [10-11]. Numerous studies have shown that Ori has a variety of pharmacological activities, such as anti-tumor, anti-inflammatory, antioxidative and antibacterial [12-14]. It has been found that Ori has significant inhibitory effects on oral cancer, ovarian cancer, colon cancer and lung cancer [15]. Its treatment of acute myeloid leukemia has entered the stage of clinical trials [16]. It has been reported that Ori is a specific covalent inhibitor of the NLRP3 inflammasome, blocking the interaction between NLRP3 and NEK7 by forming covalent bonds with the 279 cysteine of the NLRP3 NACHT domain, thereby inhibiting the assembly and activation of the NLRP3 inflammasome [17]. Therefore, Ori may have the potential to treat NLRP3 inflammatory-related diseases [18]. Next, a series of Ori derivatives have been designed and synthesized, and their activity

as NLRP3 inhibitors has been studied [19]. Therefore, the acquisition of Ori derivatives with novel structure, high efficiency and low toxicity is expected to provide a new idea for the effective treatment of NLRP3 inflammasome-related diseases [20].

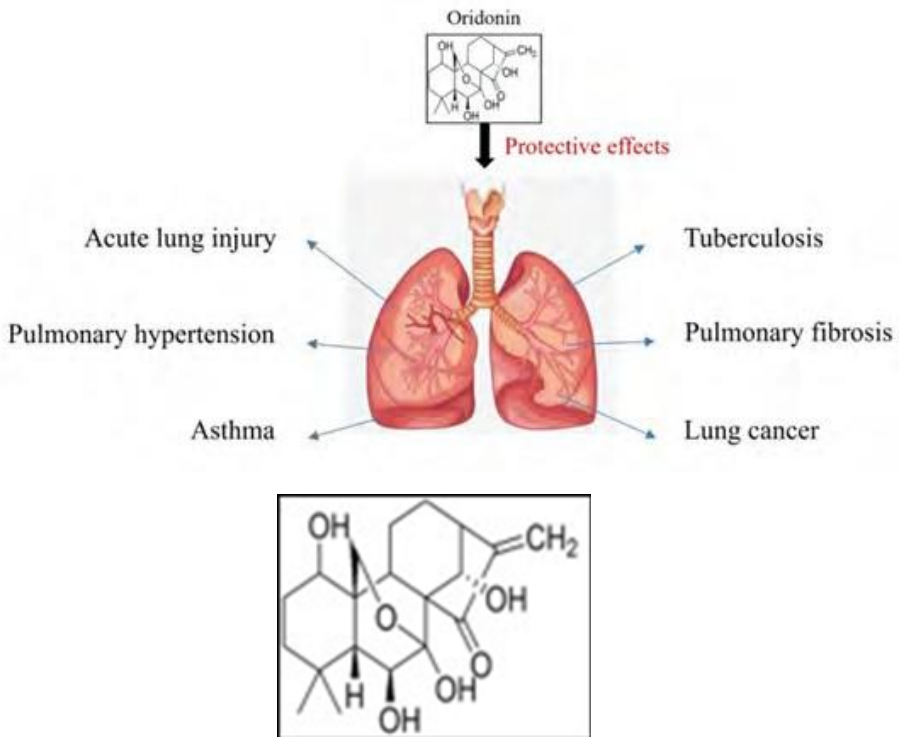

Figure 1: The Chemical Structure of Ori.

4. Activated Signaling Pathways of Ori in Lung Diseases

Ori-activated signaling pathways mostly concentrate on lung injury and lung cancer [21]. The related pathways include oxidative stress, inflammation, apoptosis and autophagy (Table 1) [22-25]. Oxidative stress occurs when the continuous generation of reactive oxygen species (ROS) overloads the ability of the organic antioxidative defense system and causes damage to DNA, proteins and lipids, which occurs in many human diseases [26]. Nrf2, as a vital nuclear transcriptional factor, shows strong antioxidative activity and has been widely used as a promoter to inhibit oxidative stress and the resulting inflammation [27, 28]. It has been shown that Ori acts as a Nrf2-activator to protect humans from various environmental insults [29, 30]. Among the various inflammatory pathways, NOD-like receptor protein 3 (NLRP3) inflammasome and nuclear factor kappa B (NF-κB) pathways play an important role [31, 32]. NF-κB can be a sensor to start the inflammatory response under some stimuli, such as ROS, FFA, and pro-inflammatory factors [33] [34]. In normal conditions, NF-κB interacts with IκB to be a state of silence and have no effect on downstream genes. However, when stimulus occurs, IκB is phosphorylated and NF-κB is released and activated to control the expressions of genes and inflammatory mediators [35]. Another significant pathway, the NLRP3 inflammasome, can be activated by the assembly of NLRP3/ASC/pro-caspase 1 protein complex, resulting in the release of IL-1β. The release of these inflammatory factors activates many of polymorphonuclear neutrophils (PMNs), inducing "respiratory burst" and producing a large amount of reactive oxygen species (ROS) [36]. Ori has been shown to be a covalent NLRP3 inhibitor with strong anti-inflammasome activity [18]. Programmed cell death is involved in the study of the pharmacological effects of Ori [15]. Autophagy, also known as 'self-eating', is the process of transporting damaged, denatured or aged proteins and organelles to lysosomes for digestion and degradation. Autophagy consists of three stages: formation of autophagosomes, fusion of autophagosome-lysosome and degradation of autophagolysosomes [37]. As a vital effector of autophagy regulation, apoptosis can be initiated to counteract the proliferation, metastasis and cisplatin resistance of cancer cells, so that many activators of apoptosis are used in cancer treatment [38].

Then we summarize the signaling pathways of Ori-activated in pulmonary diseases. The anti-inflammatory effects of Ori are mostly related to oxidative stress (Keap1/Nrf2) and inflammatory pathways (NF-κB and NLRP3) in lung injury [23]. It has been reported that Ori exerts anti-inflammatory effects via regulating Keap1/Nrf2 in LPS-induced lung injury [39]. In ventilator or silicon dioxide caused lung injury, Ori suppresses NLRP3 inflammasome and NF-κB pathways [40] [22]. In addition, hyperoxia and cecal ligation and puncture (CLP) contribute to the release of TNF-a and IL-6, which can be reversed by Ori [41]. Besides, Ori's anti-cancer effects are involved in apoptosis, autophagy, EMT and

inflammatory pathways [42] [43]. Ori inhibits the cell proliferation of lung cancer and enhances the sensitivity of radiotherapy and cisplatin by regulating apoptosis and autophagy [44] [45]. It has been demonstrated that Ori inhibits mTOR signaling and the growth of lung cancer [46]. Inhibition of p-STAT3 enhances the cytotoxicity of NK cells in lung cancer [47]. Additionally, Ori sensitizes cisplatin-induced apoptosis via AMPK/Akt/mTOR-dependent autophagosome accumulation in A549 cells [48]. Ori re-sensitizes lung cancer cells to radiotherapy by regulating autophagy, EMT and DNA damage [49].

Table 1: The therapeutic effects of Ori.

Effects	Host	Key mechanisms	References
anti-tumor	Lung cancer: A549 cells, SCLC cells (H1688 and H446)	Suppression of EGFR/ERK/ MMP-12 and upregulation of p62 and the LC3B-II/LC3B-I ratio	[73] [42]
	Gastric cancer: SGC7901/DDP cell line	Downregulation of P-gp, MRP1 and cyclin D1	[85]
	Ovarian cancer: A278/DDP and SKOV3/DDP cell lines	Downregulation of Bcl-2 and upregulation of Bax	[86]
	AML: MV4-11/DDP cell lines	Induction of apoptosis	[87]
	Colorectal cancer: HCT-15 and HCT-15/5FU-R cell line	Upregulation of ROS/JNK/c-Jun axis and induction of apoptosis	[88]
anti-inflammatory	Autoimmune Neuritis: RAW 264.7 cell line, Lewis rats	Suppression of Notch pathway	[89]
	Hepatic stellate cells	Inhibition of IKK/IκBα/NF-κB pathway	[90]
	diabetic nephropathy: HBZY-1 cells, Sprague Dawley (SD) rats	Inhibition of TLR4/p38-MAPK and TLR4/NF-κB signaling pathways	[91]
	liver injury: C57BL/6 mice	Inhibition of NLRP3 inflammasome	[92]
	Lung injury: RAW264.7 cells, C57BL/6 mice	Suppression pf NLRP3 and NF-κB pathways	[23]
antioxidative	Atherosclerosis: Apolipoprotein E-deficient (*ApoE*$^{-/-}$) mice	stabilization of Nrf2	[93]
	cardiac hypertrophy: neonatal rat cardiac myocytes, C57BL/6	Regulation of P21-related autophagy	[94]
	Liver injury: Sprague-Dawley (SD) rats	Inhibition of the activity of xanthione oxidase	[95]
antibacterial	MRSA strain	Disturbance in protein and DNA metabolism	[96]
	A. hydrophila AS 1.1801	Inhibition of hemolytic activity, lipase activity, and protease activity	[97]

5. Role of Ori in Pulmonary Diseases

Ori exerts anti-inflammatory, antioxidant, anti-fibrosis and anti-cancer effects [10]. We summarize the roles of Ori in pulmonary diseases, including acute lung injury, asthma, lung fibrosis, pulmonary hypertension, tuberculosis and lung cancer (Table 2) [22-51].

Table 2: The protective effects of Ori in pulmonary diseases.

Lung diseases	Key mechanisms	Protective effects	References
Acute lung injury	Keap1/Nrf2 pathways; TLR4/MyD88/NF-κB pathways; NLRP3 inflammasome; MAPK pathways	Anti-inflammatory and antioxidative effects	[57] [23] [40][58] [41] [22]
Asthma	regulates Th1/Th2 balance; apoptosis; NLRP3 inflammasome	Anti-inflammatory, anti-apoptosis and anti-asthmatic effects	[61] [62]
Pulmonary fibrosis	TGFβ/Smad Pathway; iNOS; impaired autophagy, oxidative stress, inflammation; EMT	Anti-inflammatory and inhibiting myofibroblast differentiation	[67] [68] [22]
Lung cancer	Bcl-2/Bax/caspase 3 pathways, FAK-ERK 1/2, P53/ CHK2; Beclin-1 activation; AMPK/Akt/mTOR-dependent autophagosome accumulation, EGFR/ERK/MMP-12 and CIP2A/PP2A/Akt pathways	Inhibiting the proliferation of tumor cells and drug resistance to chemotherapy and radiotherapy	[43] [25] [72] [49] [73] [48]
Pulmonary hypertension	mitochondria-dependent pathway	inducing smooth cell apoptosis	[51]
Tuberculosis	NRF2/HO-1/NQO-1; AKT/AMPK-α1/GSK-3β signaling pathways	antioxidative	[50]
Pleurisy	Keap-1/Nrf2 pathway; TXNIP/NLRP3; NF-kappaB pathway	antioxidative and anti-inflammatory	[75]

5.1. Ori and Acute Lung Injury

Acute lung injury (ALI)/ acute respiratory distress syndrome (ARDS) is a common cause of respiratory failure in critical patients and occurs in approximately 10% of patients in intensive care units. Although the situation has improved, there is still a lack of effective treatment and the mortality rate is still as high as 30% to 40% [52]. ALI/ARDS is an acute inflammatory process in which the infiltration of inflammatory cells leads to severe damage of alveolar epithelium and alveolar capillary membrane, increased vascular permeability, and pulmonary interstitial/alveolar edema [53]. The pathophysiology of ARDS involves multiple mechanisms, including inflammatory cell infiltration, oxidative stress, alveolar capillary barrier breakdown/permeability change, apoptosis, and tissue fibrosis [54]. It is involved in the activation of MAPK, NF-κB, AMPK/SIRT1, PI3K/Akt, Nrf2/HO-1, Wnt/β-catenin, Notch and other molecular signaling pathways [55] [56]. Current research has found that Ori shows protective effects in acute lung injury (Figure 2). Ori suppresses LPS-induced lung injury by regulating keap1/Nrf2 pathways, TLR4/MyD88/NF-κB pathways and NLRP3 inflammasome [57, 23]. In ventilator-induced lung injury, Ori inhibits the activation of NLRP3 inflammasome and release of IL-1β [40]. Besides, hyperoxia and CLP induce the activation of pro-inflammatory factors and the inhibition of antioxidant factors, which is reversed by Ori treatment [58, 41]. While silicon dioxide-induced the release of NLRP3-independent IL-1α and the activation of MAPK pathways can be restrained by the treatment of Ori [22].

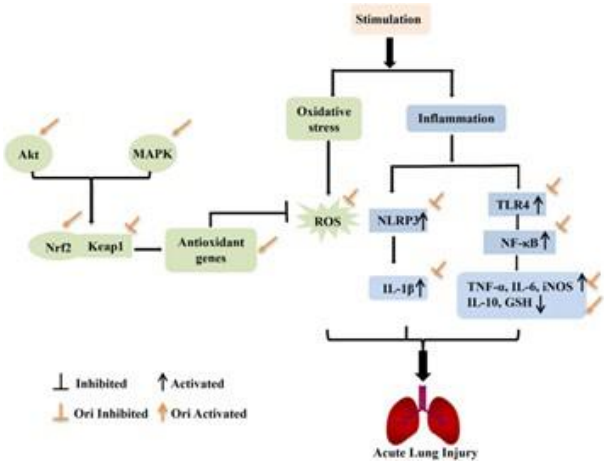

Figure 2: The potential targets and signaling pathways of Ori in acute lung injury.

6. Ori and Asthma

Asthma is a chronic inflammatory disease of the airways that affects both children and adults [59]. This chronic inflammation is associated with hyperresponsiveness of the airway, usually with a wide range of reversible airflow restrictions, and causes recurrent wheezing, shortness of breath, chest tightness, and cough [60]. The present study demonstrated that Oridonin regulates Th1/Th2 balance in mice and decreased the OVA induced airway hyperresponsiveness significantly [61]. Oridonin attenuates apoptosis and NLRP3 inflammasome activation in IL-4-stimulated human bronchial epithelial cells in a pediatric asthma model [62]. These findings indicate that Oridonin may serve as a potential therapeutic compound for the treatment of asthma in the future.

7. Ori and Pulmonary Fibrosis

Pulmonary fibrosis occurs after acute lung injury and seriously affects the prognosis of patients [63]. Studies have found that fibrosis occurs in every phase of lung injury, and the degree of fibrosis increases with time [64]. LPS and bleomycin are often used to establish models of lung injury and pulmonary fibrosis, which are used to assess effective drugs and related mechanisms [65]. Epithelial-Mesenchymal Transition (EMT), inflammation, oxidative stress and autophagy have been shown to take part in the pathological process of pulmonary fibrosis [66]. There are fewer studies about the roles of Ori in lung fibrosis. Oridonin inhibits myofibroblast differentiation and bleomycin-induced Pulmonary Fibrosis by Regulating TGFβ/Smad Pathway [67]. Additionally, Ori attenuates LPS-induced lung fibrosis by regulating impaired autophagy, oxidative stress, inflammation and EMT [68]. Moreover, Oridonin attenuates lung inflammation and fibrosis in silicosis via covalent targeting iNOS [22].

8. Ori and Lung Cancer

With the highest morbidity and mortality, lung cancer is a serious disease affecting public health. In terms of biological characteristics, lung cancer is divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for 80–85% of all lung cancers with poor prognosis [69]. At present, the standard treatment is surgery combined with chemotherapy and radiotherapy. Although it can alleviate or even cure some patients and effectively prolong survival, recurrence and metastasis are still huge obstacles in the treatment of lung cancer, seriously affecting the prognosis and median survival of patients [70]. Hence, inhibiting the proliferation of tumor cells and drug resistance to chemotherapy and radiotherapy is a difficult problem to solve [71]. Recent studies have demonstrated that Ori has anti-cancer effects in lung cancer (Figure 3). Firstly, Ori inhibits the proliferation, migration, invasion of lung cancer cells, which are associated with Bcl-2/Bax/caspase 3 pathways, FAK-ERK 1/2, P53/CHK2 and Beclin-1 activation [43, 25, 72]. Secondly, apoptosis and DNA damage take part in the pathological process of radiotherapy sensitization for non-small cell lung cancer [49]. Finally, Ori has the effects of chemotherapy sensitization, which is connected with AMPK/Akt/mTOR-dependent autophagosome accumulation, EGFR/ERK/MMP-12 and CIP2A/PP2A/Akt pathways [73, 48].

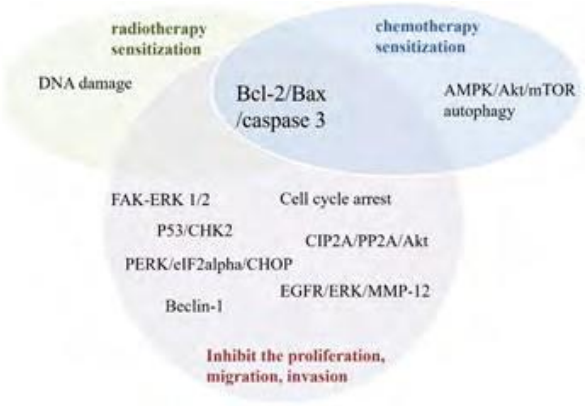

Figure 3: The potential targets and signaling pathways of Ori in lung cancer.

9. Ori and other Pulmonary Diseases

In addition, there are few investigations about the roles of Ori in pulmonary hypertension, tuberculosis and pleurisy. The results suggest that Ori can lower pulmonary artery pressure effectively, and inhibit pulmonary artery structural remodeling by inducing smooth cell apoptosis via a mitochondria-dependent pathway [51]. Ori supplementation inhibited the proliferation of Mm in zebrafish, as well as reducing oxidative stress levels in infected zebrafish [50]. Additionally, Oridonin derivatives were designed and showed significant antitubercular against Mycobacterium phlei [74]. And in carrageenan-induced pleurisy, Ori exerts protective effects via activation of the Keap-1/Nrf2 pathway and inhibition of the TXNIP/NLRP3 and NF-kappaB pathway in mice [75].

10. Conclusion and Future Perspectives

Ori is a tetracyclic diterpenoid compound derived from a natural Chinese herbal medicine, and is the main active component of the traditional Chinese medicine. Studies have found that Ori has anti-oxidative, anti-inflammation, anti-tumor, anti-apoptosis, and enhances the body immunity [10]. And it is widely used in traditional Chinese medicine to treat inflammatory diseases and malignant tumors [17, 45]. The anti-inflammatory activity of Ori has been extensively studied in various animal models, including osteoarthritis, vascular inflammation, neuroinflammation, acute liver injury, acute kidney injury, irritable bowel syndrome and other diseases [76, 77] [78]. The anti-tumor effects of Ori have been investigated in breast cancer, ovarian cancer, lung cancer and melanoma [45]. Here, we summarize the roles and related signaling pathways of Ori in diverse pulmonary diseases in this paper. The existing studies have found that Ori has protective effects on lung injury, pleurisy, asthma, tuberculosis, pulmonary hypertension, pulmonary fibrosis and lung cancer. Oxidative stress and inflammation

are the main molecular mechanisms of acute lung injury. Recent research has demonstrated that Ori acts as a Nrf2-activator and NLRP3-inhibitor to protect against lung injury caused by LPS and ventilator [23, 40]. Besides, silicon dioxide-induced the activation of TLR4/NF-κB, vascular inflammation and MAPK pathways can be reversed by Ori treatment [22]. Pulmonary fibrosis occurs in every step of lung injury. LPS and bleomycin induce the activation of collagen-I and TGF-β, the differentiation of fibroblasts and destruction of the alveolar wall [79]. Ori attenuates lung fibrosis via regulating Nrf2/NOX-4, NLRP3-dependent release of IL-1β and impaired autophagy [68]. Besides, the growing importance of NLRP3-mediated inflammatory pathways appears in pleurisy and asthma. Absolutely, Ori shows anti-inflammatory and anti-allergic effects via the inhibition of NLRP3 inflammasome [61, 75]. The oxidative imbalance might play a prior role in the pathological process of tuberculosis, and Ori regulates the activation of Akt/AMPK and Nrf2/HO-1 to inhibit the progression of tuberculosis [50]. At present, many studies are discussing the anti-cancer effects of Ori. Programmed cell death and DNA damage take part in the proliferation, migration, invasion and drug resistance of lung cancer [44, 80]. Ori inhibits lung cancer cell proliferation and enhances cytotoxicity of NK cells by inducing apoptosis [47]. Ori also improve the sensitivity of chemotherapy and radiotherapy of lung cancer cells via regulating Bax and caspase-3 [24]. Moreover, Ori induces the cell cycle arrest via the mediation of P53 [72]. Autophagy also participates in the proliferation and cisplatin-sensitivity of lung cancer cells [38]. Ori sensitizes cisplatin-induced apoptosis via AMPK/Akt/mTOR-dependent autophagosome accumulation in A549 Cells [48]. Suppression of PERK/eIF2alpha/CHOP pathway enhances oridonin-induced apoptosis by inhibiting autophagy in small cell lung cancer cells [42]. To sum up, Ori plays a vital role in pulmonary diseases. Recent studies have found that the extraction purity of Ori is low, it is difficult to dissolve, and the tissue bioavailability is low. Therefore, further study of Ori's biosynthesis pathway, using genetic engineering technology to increase Ori content, and using nanotechnology to synthesize biocompatible targeted drugs are future research directions [81, 82]. It has been reported that Ori-loaded nanoparticles are stable and easy to enter the deep lung tissue. Recent research has proved it can be used in the treatment of lung injury and lung cancer [83] [84]. Thus, more studies are urgently needed to prove the effect of Ori on pulmonary diseases and how to improve its bioavailability, which makes it enter clinical application as soon as possible.

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