



Review

Resveratrol extracted from Chinese herbal medicines: A novel therapeutic strategy for lung diseases

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ARTICLE INFO

Article history:

Received 16 April 2020

Revised 9 May 2020

Accepted 30 July 2020

Available online 18 September 2020

Keywords:

Chinese herbal medicines
 chronic obstructive pulmonary disease
 lung diseases
 pneumonia
 resveratrol

ABSTRACT

Lung diseases and their related complications represent a critical source of morbidity and mortality globally and have become a research focus in recent years. There are plenty of hazards that threaten the health of lung by exposure to external environmental stimuli, such as dust, cigarette smoke, PM2.5, air pollution and pathogen infection. These risks lead to the impairment of lung function and subsequent lung diseases including pneumonia, chronic obstructive pulmonary disease (COPD), asthma and idiopathic pulmonary fibrosis (IPF). Compared with antibiotics and corticosteroids therapies, traditional Chinese medicine prescriptions are more effective with fewer side effects. A considerable variety of bioactive ingredients have been extracted and identified from Chinese herbal medicines and are used for the treatment of different lung diseases, including resveratrol. Increasing studies have reported promising therapeutic effects of resveratrol against lung diseases by inhibiting oxidative stress, inflammation, aging, fibrosis and cancer both *in vitro* and *in vivo*. In this review, the recent progress in the studies of lung-protective effects and underlying mechanisms of resveratrol and also highlight the potency of resveratrol and traditional Chinese prescriptions containing resveratrol as promising therapeutic options were summarized for the treatment of lung and respiratory diseases.

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1. Introduction

Lung diseases, including pneumonia, chronic obstructive pulmonary disease (COPD), asthma and idiopathic pulmonary fibrosis (IPF), have become a research focus in recent years, which are asso-

ciated with substantial morbidity and mortality worldwide. Surveys of the general population indicated that there were approximately tens of millions of people have a history of respiratory and lung diseases only in the UK. Based on the data from Lancet Respiratory Medicine, there were more than 3.2 million people died due to COPD worldwide in 2015 (Sorathia, 2019). As the most frequent chronic disease of childhood, asthma led to over 300 million individuals affected and more than 30 thousand people

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died around the world in 2012 (Brightling, Gupta, Gonem, & Siddiqui, 2012). Generally, antibiotics, corticosteroids and lung transplants are the most common and accepted treatment options for patients with different lung diseases. Nevertheless, both systemic and local side effects of these therapies have been intensively reported. Worse yet, lack of healthy donated lungs and various complications, such as chronic lung allograft dysfunction, surgical complications and infection, continually influence transplant recipient survival and long-term consequence. Furthermore, it is difficult to avoid destructive autoimmune responses and consequent chronic impairment of lung function after lung transplantation. These above facts stimulate an increasing interest in new strategies that improve symptoms and complications in different lung diseases.

Traditional Chinese medicine (TCM) is an important source of clinical therapies and consists of different medicine formulas, including plant medicines, animal medicines and mineral medicines. Thus far, several traditional Chinese medicine prescriptions and active ingredients from herbal medicines have been applied to prevent acute or chronic lung diseases. Considerable research efforts have been devoted to plant medicines, which are not only directly used as therapeutic agents but also significant sources for pharmacological drug investigation and development. According to the World Health Organization (WHO) data in Germany, the annual sales of herbal medicines achieved USD\$2.432 billion in 2002. In 2011, the value of TCM output in China reached USD \$68 billion (Liu, Chuang, Lam, Jiang, & Cheng, 2015). Generally, traditional Chinese medicine prescriptions consist of two or more kinds of herbs as components, which occupy an extremely important place in clinical Chinese medicine treatment. Additionally, there are several non-drug treatments, including but not limited to Chinese medicine fumigation, acupoint sticking therapy, massage therapy and acupuncture. Importantly, the National Institutes of Health (NIH) indicated that acupuncture could be included in a synthetic management program in many diseases involving asthma. Moreover, TCM therapies have shown the advantages in treating lung disease by effectively decreasing complications and fatality, preventing complications, alleviating symptoms and improving the quality of life. In recent months, a novel coronavirus named 2019-nCoV (2019-nCoV) has broken out and spread rapidly all over the world. Meanwhile, plenty of studies have confirmed that TCM plays an increasingly important role in the treatment of coronavirus by alleviating clinical symptoms such as cough, fever and malaise.

As recorded in *Huangdi Neijing* and *Treatise on Febrile Disease*, TCM is historically applied across Asian countries, not only used for maintaining daily health, but also for treating lung diseases. According to clinical reports, TCM has been widely used in the treatment of several lung diseases, including pneumonia, asthma, lung distention and collapsed lung (Table 1). TCM is used for the treatment in the acute exacerbation stage of COPD by decreasing inflammation, transforming phlegm, activating blood circulation and releasing lung pressure. Meanwhile, previous studies also report that traditional Chinese medicine prescriptions are used for the treatment of IPF through replenishing qi and activating blood formula (Zhang, Deng, Huang, & Tan, 2014). As shown in Table 1, there are plenty of classical prescriptions, such as Qingfei Huatan Decoction, Huzhang Oral Liquid, Feiyu Granules and Baihe Gujin Pill that exert obvious therapeutic effects on the treatment of pneumonia, COPD, asthma and IPF. Notably, *Polygonum cuspidatum* Sieb. et Zucc (*P. cuspidatum*, Huzhang in Chinese) is the most frequently herbal medicine used in these prescriptions. Historically, *P. cuspidatum* was first recorded in *Ming Yi Bie Lu* and has been utilized in many herbal formulas for over 2000 years. It can be either used alone or in combination with other herbs to relieve cough, reduce sputum, dispel wind-evil and dampness. Besides, after

treatment with traditional Chinese prescriptions containing *P. cuspidatum*, clinical symptoms such as cough and asthma were eliminated and X-ray examination indicated the disappeared shadow of the lung. Previous studies also demonstrated that traditional Chinese medicine prescriptions containing *P. cuspidatum* or its water decoction ameliorated pneumonia and asthma and decreased pulmonary hypertension followed by the remission of COPD symptoms (Table 1). It has also been reported that *P. cuspidatum* significantly decreased levels of hydroxyproline in lung tissues and alleviated IPF in rats (Zhang et al., 2014). Additionally, it is also important to highlight that *Lilium brownii* var. *viridulum* (*L. brownii*, Baihe in Chinese) is another herb medicine contained in almost all of these traditional Chinese prescriptions (Table 1).

Resveratrol (3,5,4'-trihydroxy-trans-stilbene), a well-known polyphenol phytoalexin, is synthesized in several plants and has been isolated and identified in multitudinous fruits, such as grapes and berries, and the roots of Chinese herbal medicines, such as *P. cuspidatum*. Resveratrol is extensively utilized and prescribed in traditional Chinese and Japanese medicines. In addition to *P. cuspidatum*, it should be mentioned that *Morus alba* L. (*M. alba*, Sangbaipi in Chinese), *Magnolia officinalis* Rehd. et Wils. (*M. officinalis*, Houpu in Chinese), *Belamcanda chinensis* (L.) Redouté (*B. chinensis*, Shegan in Chinese) and *Panax notoginseng* (Burkill) F. H. Chen ex C. H. (*P. notoginseng*, Sanqi in Chinese) have been applied as common herbal medicines of traditional Chinese prescriptions for treating lung disease, and interestingly, all of these herbal medicines contain resveratrol (Table 1). Many studies illustrated the promising therapeutic effects of resveratrol against lung diseases mainly by decreasing oxidant stress, suppressing free radicals like reactive oxygen species (ROS) and inhibiting inflammatory responses (Wu & Huang, 2017). Furthermore, resveratrol has been characterized with anti-microbial, neuroprotective, anti-aging, cardioprotective and anti-cancer activities both *in vivo* and *in vitro* (Lee et al., 2018; Li, Li, & Lin, 2018). Most recently, resveratrol was shown to protect rat lung in the early stages after lung transplantation (Xu, Lv, Wang, Ye, & Hu, 2019). Although previous studies suggest that resveratrol or traditional Chinese prescriptions containing resveratrol has been practiced clinically to treat a variety of lung diseases, a comprehensive review with perspectives on the limitations of current pharmacology researches of resveratrol on lung diseases is still missing.

In this review, we mainly focus on the protective effects and underlying mechanisms of resveratrol on four kinds of common lung or respiratory diseases, including pneumonia, COPD, asthma and IPF. Meanwhile, this review comprehensively summarizes recent progresses, highlights findings neglected by earlier studies and provides novel insights regarding the potential use of resveratrol and traditional Chinese prescriptions containing resveratrol as promising therapeutic options for the treatment of lung disease.

2. Resveratrol and pneumonia

A spiral of pneumonia leads to frailty, infection and possible death. Equally important, academic researches and case reports of pneumonia are continuously increased worldwide. Until now, pneumonia is a significant source of mortality and morbidity around the world. In the United States, there were over 50,000 deaths as a result of pneumonia and influenza during 2015 alone (Heron, 2017). Pneumonia is a pathological reaction characterized by cough and dyspnea. Recent studies have revealed that TCM exerts a striking role in regulating immunity, improving microcirculation, suppressing mycoplasma pneumoniae, protecting epithelial cells and alleviating adverse drug reactions. Meanwhile, it has been suggested that *P. cuspidatum* can be used alone or in combination with other herb medicines to treat lung diseases (Table 1).

Among numerous natural ingredients isolated and identified in *P. cuspidatum*, resveratrol and polydatin are the highest content of stilbenes (Zhang et al., 2019).

Since December 2019, 2019-nCoV associated pneumonia has broken out and is caused by a new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The unknown β -CoV strain of SARS-CoV-2 showed 79.0% nucleotide identity with the sequence of SARS-CoV. It has been previously confirmed that SARS-CoV was the cause of SARS in 2003. Furthermore, structural analysis in recent studies suggested that these two coronaviruses were able to bind to the same angiotensin-converting enzyme 2 (ACE2) receptor in humans (Lu et al., 2020). *In vivo* experiments revealed that SARS-CoV ssRNA caused acute lung injury and high mortality in mice. Earlier reports indicated that resveratrol inhibited SARS-CoV-induced cytotoxic effects *in vitro* through directly inhibiting the replication of SARS virus (Li et al., 2006). Although there is no experimental or clinical data to support that resveratrol can inhibit SARS-CoV-2 virus replication, news from Shanghai

Institute of Medicine reveals that SARS-CoV-2 may be suppressed by several bioactive ingredients isolated from *P. cuspidatum*, which was an important source of resveratrol. These data suggest a potential therapeutic role of resveratrol in SARS-CoV-2-induced severe acute respiratory syndrome, although further experimental evidence is required.

On the one hand, *Serratia marcescens* is a nosocomial pathogen and has been recognized as an important agent of hospital-acquired pneumonia in the past two decades. Researchers found that pretreatment with resveratrol for 3 d enhanced NK cell activity, markedly elevated alveolar macrophage infiltration and reduced pneumonia via decreasing bacterial burden in the infected lung (Long et al., 2016). Activated I-kappa-B-alpha (I κ B) kinases (IKK α / β) phosphorylated and degraded I κ B to induce the nuclear translocation of nuclear factor-kappa B (NF- κ B) p65. As an evolutionarily conserved signaling molecule, phosphorylated NF- κ B p65 further enhanced the efficiency of DNA binding and provided an additional interaction site for transcriptional co-activator CBP/

Table 1
Studies of Chinese herbal medicines containing resveratrol on treatment for lung diseases.

Diseases	Chinese herbal prescriptions	Models	Outcomes	Herbs containing resveratrol	References
Pneumonia	Sangpi Qingfei Decoction	Mycoplasma pneumonia in children	Fever was alleviated after 2 d and clinical symptoms was improved after 5 d	Sangbaipi, Houpu	(Geng, Chen, & Zhao, 2005)
	Sangxing Decoction	Nosocomial pneumonia	Clinical symptoms were improved after 7 d	Sangbaipi, Dahuang	(Zhou, Ai, & Du, 2002)
	Sangbaipi Decoction	Aged patients with pneumonia	Fever and cough were alleviated and X-ray examination indicated the disappeared shadow of lung after 10 d	Sangbaipi	(Hou & Yuan, 2012)
	Banxia Houpu Decoction	Pneumonia	Temperature and white blood cell were closed to normal after 14 d	Houpu, Dahuang	(Guo, 2016)
	Huatan Sanren Decoction	Pneumonia	Fever and cough were alleviated and X-ray examination indicated the disappeared shadow of lung after 10 d	Houpu, Sangbaipi	(Feng, 2011)
	Maxing Shigan Decoction	Pediatric pneumonia	Fever and cough were alleviated after 5–7 d	Sangbaipi	(Shi, 2012)
	Qingfei Huatan Decoction	Pneumonia	Fever and cough were alleviated and X-ray examination indicated the disappeared shadow of lung after 11 d	Huzhang, Shegan	(Hua, 2015)
	Shegan Mahuang Decoction	Bronchopneumonia	Fever and cough were alleviated after 9 d	Shegan	(Jia, Peng, Feng, & Zhou, 2014)
	COPD	Qingjin Huatan Decoction	Acute exacerbation of COPD	Forced vital capacity (FVC) and forced expiratory volume 1% were improved after 10 d	Huzhang
Huzhang Oral Liquid		COPD	The level of pulmonary arterial pressure was decreased after 21 d	Huzhang	(Tang et al., 2011)
Feiyu Granules		COPD	FVC was improved and the level of serum cholesterol was decreased after 28 d	Huzhang	(Han, Zhu, Zang, & Lu, 2014)
Baihe Gujin Decoction		COPD	FVC, FEV1/FVC were improved after 29 d	Baihe	(Liu & Jiang, 2013)
Sangbaipi Decoction		Acute exacerbation of COPD	The symptoms of cough, sputum and asthma were alleviated after 30 d	Sangbaipi	(Ye & Hong, 2011)
Asthma	Houpu Dahuang Decoction	Acute exacerbation of COPD	The symptoms of cough, sputum and asthma was alleviated after 15 d	Houpu, Dahuang	(Zhou, 2016)
	Baihe Zhimu Decoction	Rat COPD model	The levels of IL-2, IL-4 and eosinophil in bronchoalveolar lavage fluid were decreased	Baihe	(Sun, An, & Qiu, 2011)
	Baihe Gujin Decoction	Cough variant asthma	The symptoms of cough were alleviated 20 d	Baihe	(Pan, 2011)
	Shegan Mahuang Decoction	Rat COPD model	The mRNA expression of HIF-1 and VEGF were decreased	Shegan	(Liu, Zou, Meo, Zhang, & Huang, 2012)
	Shema Zhichuan Liquid	Asthma	The level of plasma viscosity was decreased and lung function was improved after 14 d	Shegan	(Liu et al., 2000)
IPF	Diankuang Mengxing Decoction	Asthma	Vital capacity and symptoms were alleviated after 14 d	Sangbaipi	(Ye & Zhou, 2004)
	Buwei Huoxue Decoction	IPF	FVC and partial pressure of oxygen were improved after 3 months	Baihe	(Wu & Zhang, 2010)
	Baihe Gujin Pill	IPF	The symptoms of cough, sputum and fibrosis was alleviated after 3 months	Baihe	(Zhou, Zhou, & Wang, 2006)
	Feiluotong Mistura	Rat IPF model	The levels of fibrosis and fibronectin was decreased after 2 months	Sangbaipi, Sanqi	(Wang & Liu, 2011)
	Yifei Huaxian Decoction	IPF	The symptoms of cough and sputum was alleviated after 3 months	Sangbaipi, Sanqi	(Li & Ma, 2006)
	Compound Biejia Ruangan Prescription	Rat IPF model	Expression and activation of NF- κ B was inhibited and activation of sod and GSH-PX was increased	Sangbaipi, Sanqi	(Niu et al., 2005)

p300 to exert many biological activities (Liu et al., 2015). Emerging evidence suggests that resveratrol alleviated *Serratia marcescens*-induced acute pneumonia through suppression of I κ B phosphorylation and NF- κ B activation in rats (Lu, Lai, Hsieh, & Chen, 2008). On the other hand, resveratrol is an alternative agent for the precaution and treatment of *Staphylococcus aureus*-associated pneumonia. It is well-established that Nod-like receptor (NLR) family pyrin domain containing-3 (NLRP3) inflammasome is a caspase-1-triggering multiprotein complex that plays an essential role in the progression of inflammatory diseases via regulating the release of cytokines. The previous report demonstrated that resveratrol improved *S. aureus*-induced pneumonia in mice by significantly decreasing the mRNA and protein expression of Caspase-1, NLRP3 and apoptosis-associated speck-like protein (ASC) (Wu & Huang, 2017). It has been well documented that NF- κ B expression and relative NLRP3 targets are regulated by p38 mitogen-activated protein kinase (p38 MAPK), c-Jun N-terminal kinases 1 and 2 (JNK1/2) and activator protein 1 (AP-1) signaling pathways in various cell types. Interestingly, further studies have indicated that resveratrol not only suppressed the *S. aureus*-upregulated phosphorylation of c-Src, platelet-derived growth factor receptor (PDGFR), p38 MAPK, JNK1/2 and AP-1, but also inhibited the expression of vascular cell adhesion molecule-1 (VCAM-1) in human lung epithelial cells (Lee et al., 2018).

Cigarette smoke (CS) has become another major cause of lung disease including pulmonary inflammation. *In vivo* experiments showed that resveratrol treatment diminished CS-induced lung inflammation by decreasing DNA binding activity of NF- κ B and elevating the expression and activity of heme oxygenase-1 (HO-1) in mice (Liu et al., 2014). It is generally accepted that PM_{2.5} is the main particulate air pollutant that related to CS. Numerous studies have reported exposure to particulate matter of < 2.5 μ m (PM_{2.5}) may trigger lung injury and pulmonary disease. Consistently, resveratrol administration abolished PM_{2.5} exposure-induced lung inflammation and fibrosis by inhibiting the activation of NLRP3 inflammasome and preventing autophagic process in the lung. In addition, resveratrol alleviated PM_{2.5}-induced cytotoxicity and diminished interleukin (IL)-1 β production in BEAS-2B cells (Ding et al., 2019).

3. Resveratrol and chronic obstructive pulmonary disease

COPD is a lung disease characterized by continuous and irreversible respiratory symptoms, including dyspnea, cough, nasal congestion, more sputum, chest tightness and persistent inflammation. It is well established that mucus hypersecretion caused by chronic airway and lung parenchyma inflammation is a common feature in COPD. The main reason for excessive mucus includes CS exposure, acute and chronic bacterial infection or viral infection. Epidemiological data indicated that COPD was a leading cause of death, accounting for more than 3 million in 2012, and it will become the third leading cause of death worldwide by 2020 (Kim & Criner, 2013). Hence, the identification and evaluation of novel therapeutic targets for the treatment of COPD are urgent.

Pulmonary rehabilitation is a treatment that ameliorates the psychological and physical condition of patients with COPD by uniting exercise regimen and education about self-care. It is generally accepted that pulmonary rehabilitation is an effective therapy for patients with COPD and improve their health-related quality of life. However, present treatments are not capable of completely suppressing inflammation and delaying disease progression associated with COPD. Sirtuin1 (SIRT1) is an NAD⁺-dependent type III histone/protein deacetylase that regulates cellular senescence, inflammation and stress resistance. Recently, there are several studies illuminated that resveratrol is an activator of SIRT1 and

might mitigate COPD by activating the SIRT1 pathway (Fig. 1). AMP-activated protein kinase (AMPK) is associated with the regulation of energetic metabolism, insulin resistance and inflammation. Qi et al. indicated that the expression of AMPK was markedly reduced, which led to the dysfunction of muscle metabolism in COPD rats. They also found that SIRT1 stimulated AMPK expression under the moderate concentration of resveratrol (Qi et al., 2014). These studies suggest that resveratrol-induced SIRT1 serves as a therapeutic target for the treatment of COPD. The p53 tumor suppressor protein controls cell cycle, apoptosis, DNA repair and oncogenesis by regulating a variety of target genes. Recent studies indicated that SIRT1-induced alternative reading frame (Arf) decreased the ubiquitinating activity of murine double minute 2 (MDM2) against p53, further suppressed macrophage activation and inflammation (Nakamura et al., 2017). Additionally, alveolar epithelial type 2 cells (AEC2) senescence was regulated by the SIRT1/p53 signal pathway and was involved in the pathogenesis of COPD. Navarro et al. demonstrated that resveratrol treatment maintained AEC2 integrity by stimulating SIRT1 expression, promoting p53 destabilization, activating phosphorylated-protein kinase B (p-Akt) and p-MDM2 signaling in COPD mouse model (Navarro, Reddy, Lee, Warburton, & Driscoll, 2017).

Evidence so far also focuses on the role of oxidative stress in the progression of lung diseases. It should be pointed out that SIRT1 promotes cell survival by reducing oxidative stress. Activated SIRT1 increases peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α) activity, subsequently upregulates the expression of target antioxidant genes, including catalase (CAT), superoxide dismutase 1 (SOD1) and SOD2 and further protects against oxidative stress (Wang, He et al., 2018; Wang, Wan et al., 2018). A previous study showed that resveratrol reduced oxidative damage in mice by activating nuclear SIRT1 and triggering ROS detoxifying enzyme, SOD2 (Sebori, Kuno, Hosoda, Hayashi, & Horio, 2018). Wang et al further reported that resveratrol prevented oxidative stress in COPD module rats by upregulating the expression of SIRT1 and PGC-1 α (Wang, Li, Li, Miao, & Xiao, 2017). Nuclear erythroid-related factor 2 (Nrf2) is a transcription factor involved in the inducible expression of a series of antioxidant and detoxification enzymes, including glutamate-cysteine ligase (GCL), which plays a key role in the process of cellular survival and defense pathway against oxidative stress. It has been reported that CS triggered oxidative stress and decreased glutathione (GSH) levels in alveolar epithelial cells. However, resveratrol treatment restored CS-induced diminish of GSH levels via activating the Nrf2 and GCL in human lung epithelial cells, indicating that resveratrol played an antioxidant role in the treatment of COPD (Kode et al., 2008).

The crosstalk between oxidative stress and inflammation in alveolar macrophages are instrumental in the pathogenesis of COPD. Recently, emerging evidence indicates that some important cytokines may also participate in the process of inflammasome formation and chronic inflammation associated with COPD. It is well-established that many cells, like epithelial cells or macrophages, secrete cytokines by CS stimulation and then result in inflammatory cell recruitment and tissue destruction. Also, cytokines regulate immunity and inflammation in COPD through autocrine, paracrine, or endocrine features. It has been renewed interest regarding the resveratrol-induced protective effects by decreasing pro-inflammatory cytokines. An increasing number of researches have recently implicated that tumor necrosis factor- α (TNF- α) was a multifunctional cytokine in inflammation and oxidative stress. Besides, IL-6 family cytokines are the common signaling receptor subunit glycoproteins, which play critical biological functions, such as stimulating B-cell and inducing host response to respiratory infections. Further study showed that the inhalation of co-spray dried resveratrol and budesonide not only prevented

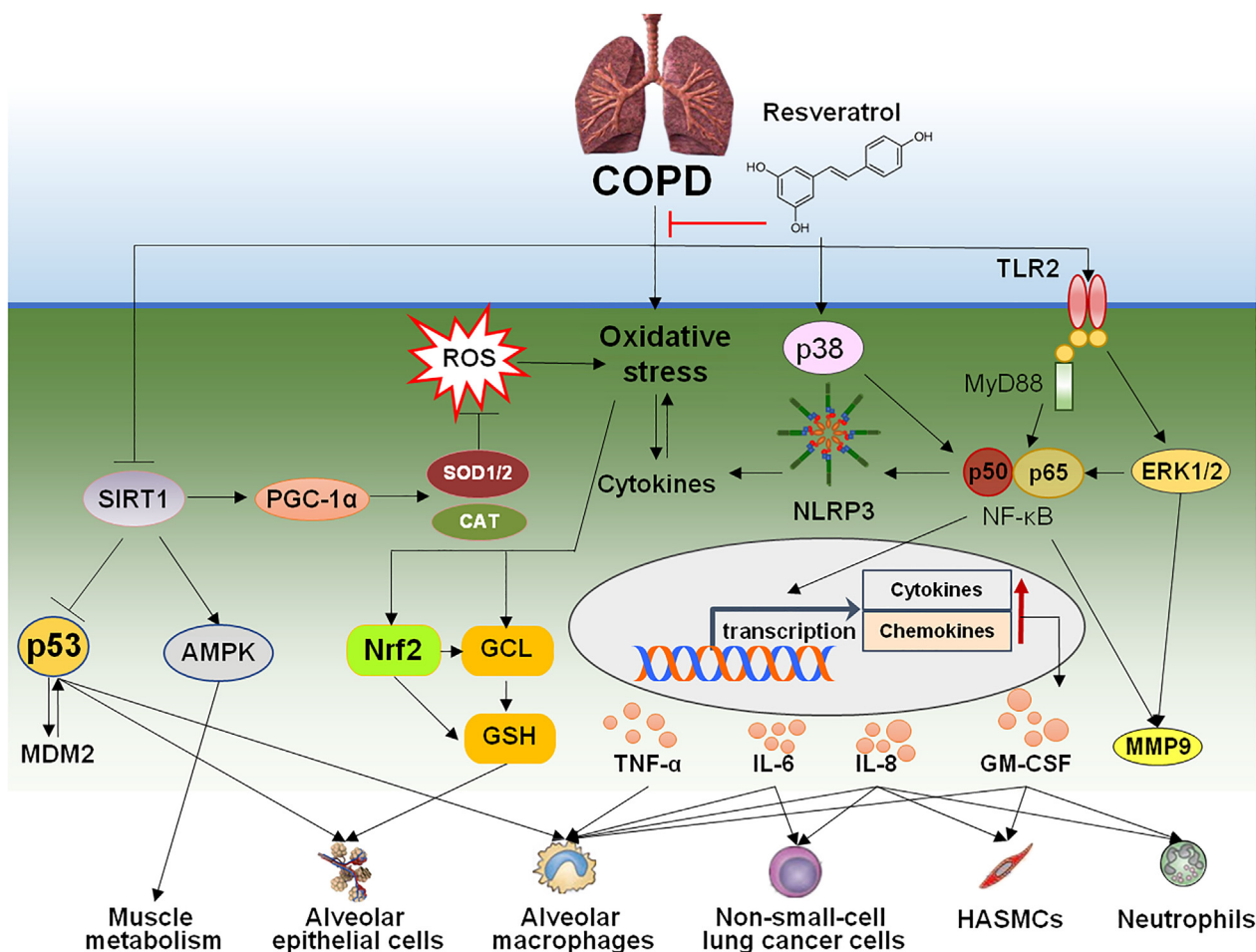


Fig. 1. Protective role of resveratrol in COPD.

oxidative stress, but also suppressed inflammation in rat alveolar macrophages via diminishing the levels of TNF- α and IL-6 (Trotta et al., 2016). It is becoming gradually clear that granulocyte-macrophage colony-stimulating factor (GM-CSF) also contributed to the augmentation of COPD by triggering inflammation and multiplying the number of neutrophils. Furthermore, IL-8, a major mediator for T-cell inflammatory responses, was markedly increased in the sputum of patients with COPD and played an important role in airway remodeling by stimulating the synthesis of collagen. Human airway smooth muscle cells (HASMCs) have been recognized as a major source of COPD-related cytokines and chemokines. GM-CSF participated in the regulation of HASMC proliferation, increased airway smooth muscle mass and caused the bronchial obstruction. Furthermore, neutrophils in lung tissue secreted several serine proteases by IL-8 recruiting and triggered alveolar destruction (Knobloch et al., 2019). Knobloch et al. verified that resveratrol impaired the release of IL-8 and GM-CSF from HASMCs through the blockade of p38 MAPK (Knobloch et al., 2010). Furthermore, *in vitro* experiments demonstrated that the release of IL-8 and GM-CSF were stimulated by IL-1 β or CS in alveolar macrophages isolated from bronchoalveolar lavage (BAL) fluid from patients with COPD. In addition, resveratrol decreased IL-1 β stimulated release of IL-8 and GM-CCF to basal levels (Culpitt et al., 2003). These results suggested that resveratrol might become an effective pharmacotherapy for macrophage pathophysiology in COPD by inhibiting inflammatory cytokine release. In nickel-induced human bronchial epithelial (BEAS-2B) cells, resveratrol significantly prevented cell apoptosis, decreased oxidative stress

and expressions of TNF- α , IL-1 β , IL-6 and IL-8 through inhibiting p38 MAPK, NF- κ B and NLRP3 pathways (Cao et al., 2020). Another *in vitro* experiment illustrated that serum obtained from COPD patients stimulated the migration of non-small-cell lung cancer cells (A549). Interestingly, resveratrol ameliorated cytokine production and oxidative stress via markedly inhibiting IL-8 and IL-6 production in A549 cells (Gauliard et al., 2008).

Matrix metalloprotease-9 (MMP-9) not only plays crucial roles in tumor metastasis but also is involved in the development of COPD by inducing neutrophil chemotaxis, extracellular matrix degradation and inflammation. The further study implied that after lipopolysaccharide (LPS) treatment, the levels of IL-8 and MMP-9 were increased, however, the levels of IL-6, GM-CSF and monocyte chemoattractant protein 1 (MCP-1) did not increase in alveolar macrophages isolated from COPD patient. In contrast, the release of all cytokines and MMP-9 was completely reduced by resveratrol treatment (Knobloch, Hag, Jungck, Urban, & Koch, 2011). Inflammatory stimulus triggered NF- κ B translocated to the nucleus and subsequently increased the expression of cytokines and MMP-9. *In vitro* experiments showed that the ratio of NF- κ B-positive cells and concentrations of TNF- α and MMP-9 were increased in COPD lymphocytes. Meanwhile, resveratrol treatment significantly reduced the ratio of NF- κ B-positive cells and the concentration of TNF- α and MMP-9 in lymphocytes isolated from COPD patients (Liu, Bao, Zeng, & Wei, 2016). *Haemophilus influenzae* (NTHi) is a major respiratory pathogen that leads to exacerbating COPD. NTHi combined with toll-like receptor (TLR) on epithelial cells and booted a signaling cascade, including the production of antimicro-

bial peptides, cytokines and chemokines. The adaptor protein myeloid differentiation factor 88 (MyD88) activated NF-κB and MAPK signaling pathways to reinforce the inflammatory response by TLR2 activation. It has been demonstrated that resveratrol significantly enhanced NTHi-induced MyD88 by inhibition of ERK1/2 activation. The expressions of cyclic adenosine monophosphate (cAMP), protein kinase A (PKA), mitogen-activated protein kinase phosphatase-1 (MKP-1) in the airway epithelial cells and in the lung of mice with COPD were also significantly decreased by resveratrol treatment (Andrews, Matsuyama, Lee, & Li, 2016).

4. Resveratrol and asthma

Asthma is a common disease caused by chronic inflammation of the lower respiratory tract, which is characterized by variable airway obstruction and bronchial hyperresponsiveness. Meanwhile, the clinical symptoms of asthma are shortness of breath, chest tightness, cough, and episodes of wheeze. Although asthma can maintain normal and quiescent in a long period, remodeling and inflammatory processes change the bronchial milieu and predispose to acute and occasionally severe clinical reactions. What is more, with the influence of various genetic, epigenetic and environmental factors, asthma exacerbations may increase the incidence of respiratory diseases and induce a greater loss of lung function. Short-acting Beta2 agonist (SABA) bronchodilators combined with low-dose inhaled corticosteroids (ICS) can be used in the treatment of mild asthma in clinic (O’Byrne et al., 2018).

Exposure to indoor and outdoor pollutants, innate immune activation is a significant determinant of asthma severity. Previous studies showed that resveratrol frustrated airway inflammation and airway hyperreactivity (AHR) induced by OVA in several murine models of asthma (Fig. 2). It has been reported that OVA-specific IgE, IgG2a, and Th2 inflammatory cytokines, such as IL-4 and IL-5, were effectively decreased by resveratrol treatment. Moreover, resveratrol also significantly suppressed mucus hypersecretion, AHR, and eosinophilia (Lee et al., 2009). In OVA-induced mouse model, resveratrol was found to markedly reduce the serum levels of IL-5, IL-13 and TGF-β, decrease total cell counts of CD3⁺CD4⁺, CD3⁺CD8⁺ and CD3⁺CD4⁺IL-4 (Th2 cells) in lungs through downregulating miR-34a and subsequent inducing FOXP3, a critical mediator of T regulatory cell (Treg) functions (Alharris et al., 2018).

Concurrently, another study demonstrated that resveratrol prevented the progression of asthma through upregulating phosphatase and tensin homolog (PTEN) and SIRT1 signaling pathway. Furthermore, PTEN overexpression reduced the area of smooth muscle, inner airway wall and mucous glands, and further improved asthma, which was prevented by SIRT1 inhibitor and shRNA (Chen et al., 2015). Transforming growth factor-β1 (TGF-β1) binds to TGF receptors and activates mothers against decapentaplegic homolog (Smad) pathway, which promotes the synthesis and accumulation of extracellular matrix (ECM) and results in fibrosis. It is commonly known that the development of epithelial-mesenchymal transition (EMT) in lung tissues is associ-

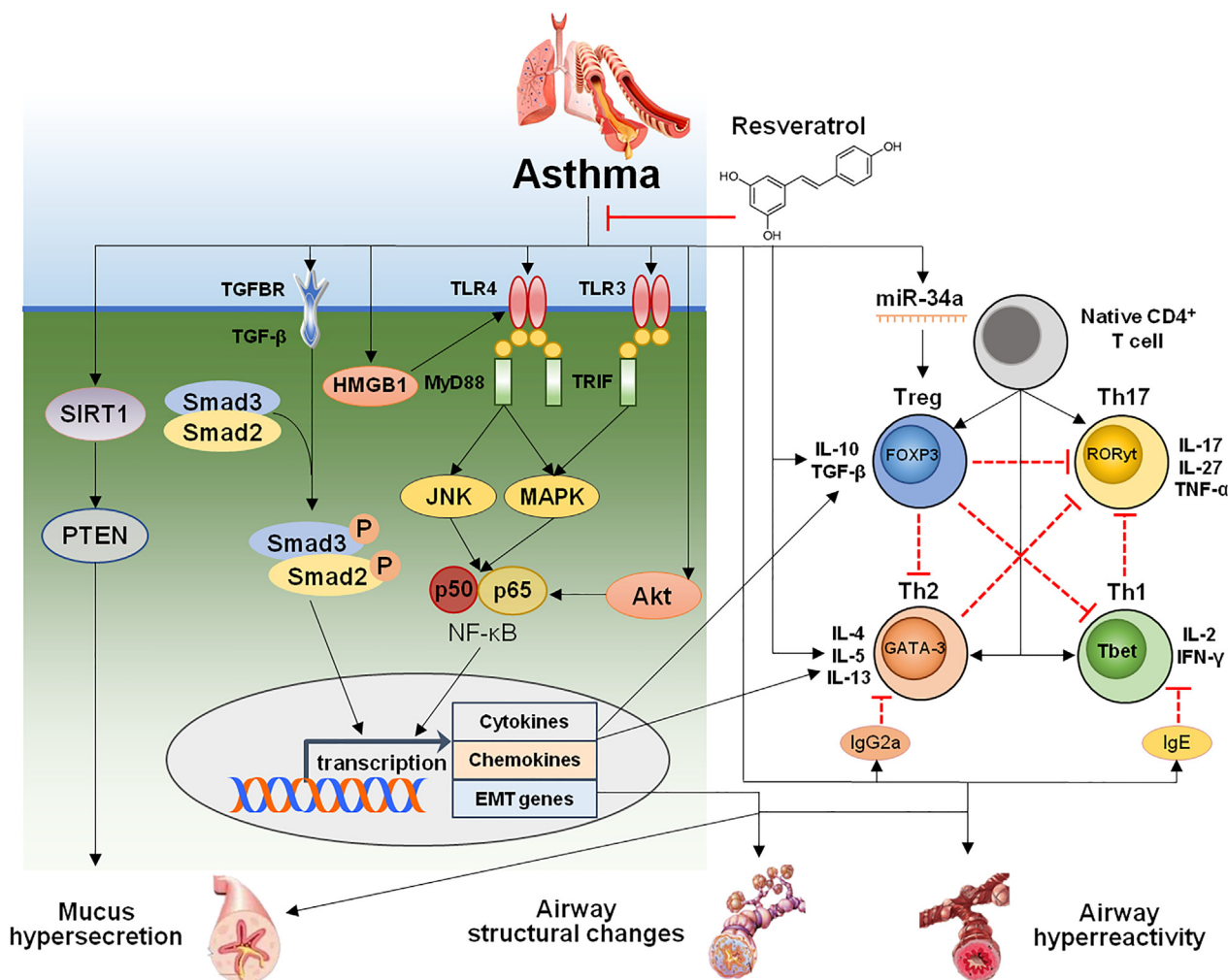


Fig. 2. Molecular targets of resveratrol in progression of asthma.

ated with the increased α -smooth muscle actin (α -SMA) expression and decreased E-cadherin expression. In addition, resveratrol effectively ameliorated airway structural changes and inflammation in a murine model of bronchial asthma via decreasing TGF- β 1 expression and then suppressing TGF- β 1/Smad2/3 signaling as well as the EMT process (Lee et al., 2017). Under the stimulus of IL-1 or TNF- α , high mobility group box 1 (HMGB1) was released by macrophages, mononuclear cells and other immune cells, activated TLR2 and TLR4, which further resulted in inflammatory response by targeting NF- κ B (Liu et al., 2020). Recently, researchers found that after resveratrol treatment, multiple inflammatory cell infiltration into the airway epithelium and airway collagen deposition was decreased. Besides, resveratrol decreased serum levels of inflammatory cytokines, including IL-1, IL-10 and TNF- α , through decreasing HMGB1/TLR4/NF- κ B pathway in OVA-induced asthma rat model (Jiang, Duan, Xu, & Zhang, 2019).

Besides, emerging studies reported the therapeutic effects of resveratrol in the treatment of asthma in other mouse models. Respiratory syncytial virus (RSV) infections cause lower respiratory tract infections of children and also play an important role in old people with asthma. Recent studies have indicated that RSV-mediated airway inflammation and AHR were alleviated by resveratrol via regulating TLR3 expression and suppressing the TRIF signaling pathway in mice (Zang et al., 2011). Insulin signaling transmission in the lungs plays an essential role in obesity-associated asthma exacerbations. Recently, researchers found that after resveratrol treatment, OVA-challenged pulmonary eosinophil infiltration and insulin resistance in obese mice were markedly abrogated. Resveratrol also significantly increased the phosphorylated AMPK expression, reduced the expression of p47phox and TNF- α and prevented ROS production in lung tissues of obese mice (Andre et al., 2016). Furthermore, another study demonstrated that

resveratrol administration improved allergic airway inflammation and obesity-associated asthma exacerbations by restoring insulin-induced phosphorylation of Akt, insulin receptor substrate 1 (IRS-1) and insulin receptor β (IR β), decreasing JNK and NF- κ B signaling pathways in lung tissues of obese mice (Andre et al., 2017).

5. Resveratrol and idiopathic pulmonary fibrosis

IPF is a chronic and fibrotic lung disease characterized by progressive scarring of the lungs and is the pathological hallmark of usual interstitial pneumonia. Excessive deposition of ECM proteins further leads to the destruction of lung structure and function, disrupted gas exchange and ultimately fatal outcome. IPF is associated with an inevitable recession in lung function, later, superimposed complications lead to the rapid exacerbation of clinical courses in IPF patients. Two anti-fibrotic medications, pirfenidone and nintedanib are sanctioned for the treatment of patients with mild to moderate IPF over the last 5 years (Tran & Suissa, 2018).

An increasing number of studies have been affirmed that resveratrol treatment is an ideal method to alleviate IPF (Fig. 3). TGF- β 1 is shown to regulate mRNA and protein expression of α -SMA through the Smad2/3 pathway and also promote the phosphorylation of Akt and ERK1/2 signaling pathways (Heldin & Moustakas, 2016). Fagone et al. investigated the effects of resveratrol on TGF- β -induced activation of human pulmonary fibroblasts into myofibroblasts. They found that resveratrol repressed TGF- β -induced collagen production, lung fibroblast proliferation and inhibited the mRNA and protein levels of α -SMA through inhibiting the phosphorylation of ERK1/2 and Akt and restoring PTEN expression (Fagone et al., 2011). Further studies demonstrated that resveratrol treatment downregulated TGF- β 1 levels, decreased

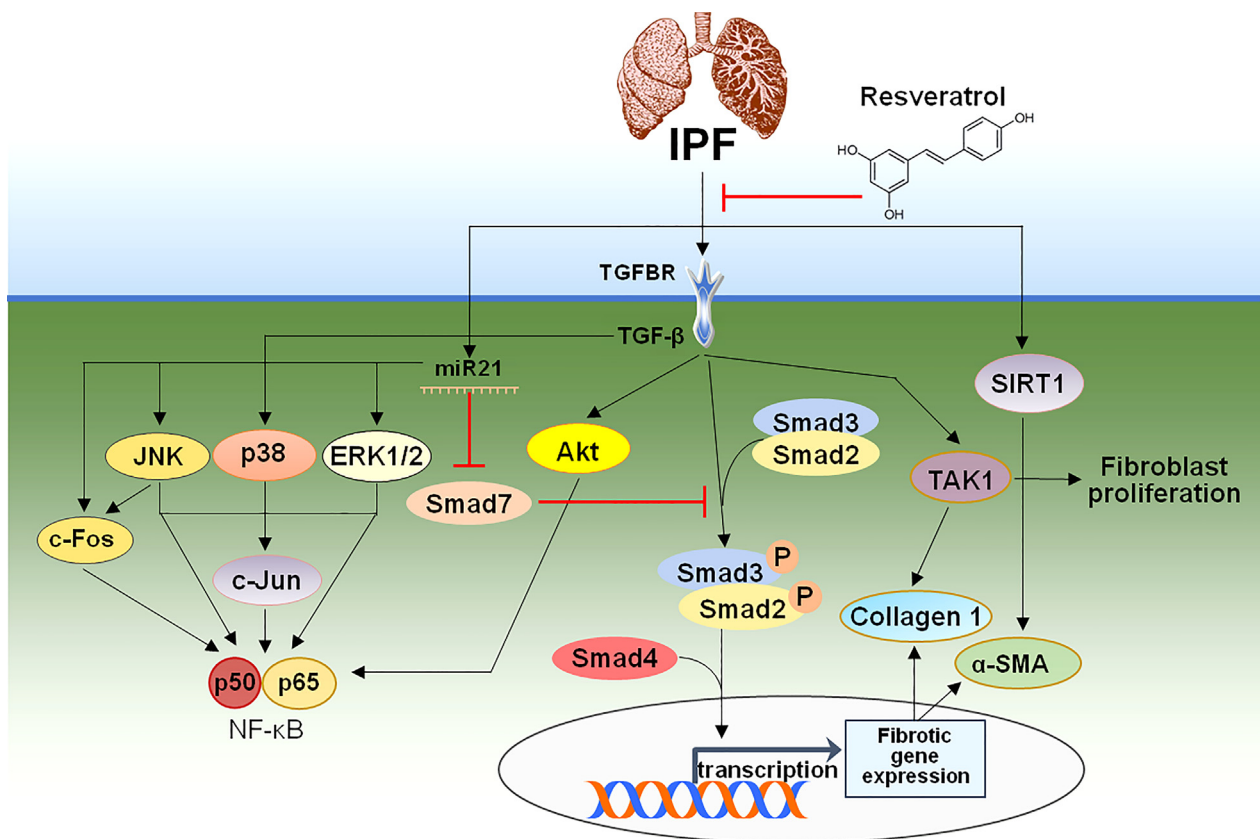


Fig. 3. Molecular targets of resveratrol in progression of IPF.

the activities of SOD and CAT and ameliorated pulmonary fibrosis in the LPS-induced mouse model via suppression of TGF- β 1/Smad2/3/4 signaling pathway (Zhang et al., 2015). In addition, miR-21 was significantly induced in bleomycin (BLM)-induced lung fibrosis model and in the lungs of patients with IPF. The pro-fibrotic role of miR-21 in lung fibrosis was through inhibiting the expression of an inhibitory Smad, Smad7 (Liu et al., 2010). Recently, it has also been reported that resveratrol treatment significantly improved BLM-induced lung fibrosis through reducing the levels of p-c-Jun, c-Jun and c-Fos, downregulating TGF- β -induced phosphorylation of Smad2/3 and increasing the phosphorylation of ERK, JNK and p38 in the rat model. These resveratrol-induced protective effects were completely inhibited by miR-21 agomir injection (Wang, He et al., 2018; Wang, Wan et al., 2018).

SIRT1 also regulated target gene expression via deacetylating a comprehensive range of transcription factors and coregulators. A previous study demonstrated that resveratrol inhibited BLM-induced EMT-associated lung fibrosis by decreasing the expression of E-cadherin, collagen I and α -SMA in the lung of mouse model, which might be associated with the activation of SIRT-1 (Rong et al., 2016). However, specific underlying mechanisms remain to be clarified. During fibrogenesis, TGF- β -activated kinase 1 (TAK1) participates in fibroblast proliferation, collagen deposition and scar formation. Li and colleagues performed microarrays and CRISPR/Cas9-based methods and revealed the important role of TAK1 in the progression of inflammation and lung fibrosis in experimental pneumoconiosis. Interestingly, *in vitro* experiments showed that resveratrol targeted TAK1 at both N161 and A107 residues and significantly inhibited TAK1 activation to alleviate inflammation and lung fibrosis (Li et al., 2017). These results suggested a potential involvement of resveratrol in the regulation of EMT, fibroblast proliferation, collagen deposition and lung fibrosis.

Furthermore, several clinical and experimental studies indicate that the incidence and severity of IPF are influenced by cellular alterations and age. Genetically, epigenetic methylations and general genetic mutations accumulated over a person's lifespan, while the expression of miRNA changed from birth to adulthood. These age-related alterations may result in gene deregulation, activated oxidative stress and accumulation of dysfunctional organelles, resulting in the development of lung disease. It has been well established that several proteases, cytokines and growth factors were secreted by injured epithelial cells, which further promoted the migration, activation and proliferation of fibroblasts and finally contributed to lung injury (Zhao, Wang, Qiu, Liu, & Yao, 2020). Resveratrol has been reported to be involved in the regulation of lifespan, health maintenance and age-associated disorders (Li et al., 2018). Additionally, resveratrol is a potential method for slowing aging-related exacerbation of lung function and structure by keeping AEC2 integrity (Navarro et al., 2017).

6. Conclusion and future perspectives

From ancient times until now, *P. cuspidatum* is one of the most effective and frequently used herbal medicine in traditional Chinese prescriptions and is prescribed for the treatment of lung diseases. A variety of clinic reports and experimental studies have been investigated the medicinal properties of crude extracts from *P. cuspidatum*. However, among the major and most representative ingredients isolated from *P. cuspidatum*, there is seldom a report highlight the importance of resveratrol in the treatment of acute or chronic lung diseases. In the present review, we comprehensively reviewed these findings. The oxidative stress and inflammation in alveolar macrophages play a key role in the pathogenesis and progression of lung disease. As a natural product isolated from various fruits and herbs, resveratrol elevated alveolar macrophage

infiltration, alleviated the oxidative stress progression and improved the inflammation process by regulating MAPK/IKB/NF- κ B, HMGB1/TLR4/NF- κ B and SIRT1/PGC-1 α pathway, which further protected the lung from external stimuli. On the other hand, resveratrol also inhibited the release of many cytokines and suppressed lung inflammation in mice by significantly decreasing the levels of Caspase-1, NLRP3 and ASC, regulating p38 MAPK/JNK1/2/AP-1 and ERK1/2/MyD88 signaling pathways. It also exerted protective effects on lung diseases by significantly suppressing mucus hypersecretion, AHR, and eosinophilia. More intriguingly, resveratrol was reported to inhibit fibroblast activation and lung fibrosis by directly reducing TGF- β /Smad2/3/4 pathway or interacting with several miRNAs.

There are several factors lead to lung diseases, such as CS, air pollution and aging. Indeed, age is a significant and inevitable risk factor for chronic diseases, especially for lung diseases, which is often overlooked in clinical practice. Therefore, it should be emphasized that the understanding of lung aging is an important part of a total strategy to lengthen life, reduce illness and enhance health. Numerous studies have confirmed that SIRT1 is associated with plenty of processes that affect life span, including inflammation, cellular senescence, cell cycle control, oxidative stress and energy metabolism. It is well established that SIRT1 expression can be upregulated through caloric restriction or pharmacological activators, particularly, natural product resveratrol. As mentioned in the section about resveratrol and COPD, AMPK serves as a therapeutic target for the treatment of patients with COPD. It has been demonstrated that SIRT1 enhanced the resistance to oxidative stress in lung tissue and overexpression of SIRT1 significantly diminished protein and lipid peroxidation caused by acute CS exposure. Previous studies have been demonstrated that the bioactivities of AMPK and SIRT1 are reciprocally interdependent. AMPK could enhance SIRT1-dependent pathways by various mechanisms, including but not limited to disrupting the interaction between SIRT1 and deleted in breast cancer 1 (DBC1) (Nin et al., 2012). On the other hand, SIRT1 mediated the deacetylation of LKB1, an upstream kinase for AMPK, transferred its location to the cytoplasm and further promoted the activation of AMPK (Lan, Cacicedo, Ruderma, & Ido, 2008). Moreover, SIRT1 was associated with the deacetylation of several transcription factors and cofactors, such as p53, PGC-1, and NF- κ B, which participated in the process of cell senescence and progression of lung diseases. However, there is still a lack of knowledge about the molecular mechanisms of resveratrol responsible for lung disease by activating SIRT1. Further studies are still required to address these concerns.

In summary, lung disease is one of the most important health issues that directly affect the life quality of patients and antibiotics are the commonly used drugs in the treatment of lung disease clinically. However, the long-term use of antibiotics is causing many inevitable side effects. Besides that, current pharmacological treatments are still inadequate to reduce the progression and mortality of lung disease worldwide. Notably, traditional Chinese prescriptions have substantial therapeutic effects with rare side effects on several chronic diseases, including lung diseases. Compared with conventional treatments, bioactive natural ingredients derived from natural herbs may provide additional benefits in the prevention of lung diseases, including pneumonia, COPD, asthma and IPF, and represent an important source of novel drug screening and development. Resveratrol is a potential and beneficial drug candidate, which has drawn a great deal of attention due to its potent anti-microbial, neuroprotective, anti-aging, cardioprotective and anti-cancer activities. Further extensive evaluation of the bioactivities of resveratrol, identification of specific molecular-target as well as structure-activity relationship is urgently needed. Further pharmacology research will contribute to the development of resveratrol or traditional Chinese prescrip-

tions containing resveratrol not only as a potential health supplement but also as health-promoting medicines in the near future.

Authors contributions

Dr. X. Li conceived the original idea. Dr. X. Li and Ms. B. Ma wrote the manuscript. Ms. B. Ma revised figures and Table 1.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by grants from Beijing Nova Program of Science & Technology (Grant NO. Z191100001119088 to XL); Beijing University of Chinese Medicine Specific Grant for “double top construction”(Grant NO. 1000041510168 to XL).

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