

# Chinese Herbs and Repurposing Old Drugs as Therapeutic Agents in the Regulation of Oxidative Stress and Inflammation in Pulmonary Diseases

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**Abstract:** Several pro-inflammatory factors and proteins have been characterized that are involved in the pathogenesis of inflammatory diseases, including acute respiratory distress syndrome, chronic obstructive pulmonary disease, and asthma, induced by oxidative stress, cytokines, bacterial toxins, and viruses. Reactive oxygen species (ROS) act as secondary messengers and are products of normal cellular metabolism. Under physiological conditions, ROS protect cells against oxidative stress through the maintenance of cellular redox homeostasis, which is important for proliferation, viability, cell activation, and organ function. However, overproduction of ROS is most frequently due to excessive stimulation of either the mitochondrial electron transport chain and xanthine oxidase or reduced nicotinamide adenine dinucleotide phosphate (NADPH) by pro-inflammatory cytokines, such as interleukin-1 $\beta$  and tumor necrosis factor  $\alpha$ . NADPH oxidase activation and ROS overproduction could further induce numerous inflammatory target proteins that are potentially mediated via Nox/ROS-related transcription factors triggered by various intracellular signaling pathways. Thus, oxidative stress is considered important in pulmonary inflammatory processes. Previous studies have demonstrated that redox signals can induce pulmonary inflammatory diseases. Thus, therapeutic strategies directly targeting oxidative stress may be effective for pulmonary inflammatory diseases. Therefore, drugs with anti-inflammatory and anti-oxidative properties may be beneficial to these diseases. Recent studies have suggested that traditional Chinese medicines, statins, and peroxisome proliferation-activated receptor agonists could modulate inflammation-related signaling processes and may be beneficial for pulmonary inflammatory diseases. In particular, several herbal medicines have attracted attention for the management of pulmonary inflammatory diseases. Therefore, we reviewed the pharmacological effects of these drugs to dissect how they induce host defense mechanisms against oxidative injury to combat pulmonary inflammation. Moreover, the cytotoxicity of oxidative stress and apoptotic cell death can be protected via the induction of HO-1 by these drugs. The main objective of this review is to focus on Chinese herbs and old drugs to develop anti-inflammatory drugs able to induce HO-1 expression for the management of pulmonary inflammatory diseases.

**Keywords:** inflammatory mediators, tracheal smooth muscle cells, pulmonary alveolar epithelial cells, ROS, Nrf2, HO-1

## Introduction

### Role of Reactive Oxygen Species in Pulmonary Inflammatory Diseases

Reactive oxygen species (ROS) can be internalized in the human body by direct inhalation or can be derived from the chemical processes of various enzymatic reactions. ROS are important for killing invading microorganisms and are also

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essential for many physiological functions. Increased generation of ROS, including hydroxyl radicals, hydrogen peroxide, and superoxide anion, have been found in individuals with chronic obstructive pulmonary disease (COPD) and asthma.<sup>1,2</sup> Among lung diseases, many types of cells, including eosinophils, neutrophils, macrophages, and antigen-presenting cells (APCs), have exhibited increased ROS production.<sup>3</sup> In our studies, we found that exposure to cytokines, endotoxins, or cigarette smoke extract in respiratory resident cells such as pulmonary alveolar epithelial cells and tracheal smooth muscle cells leads to the expression of various inflammatory mediators via induction of ROS.<sup>4–9</sup> These studies indicate that mitochondria, microsomes, and enzymes are all sources of ROS production, especially phagocytic cells, which produce large amounts of ROS when they are activated.<sup>10</sup> Therefore, ROS play a prominent role in the pathogenesis of various pulmonary disorders, in particular when the cells and tissues are exposed to environmental pollutants, infections, inflammatory reactions, or decreased levels of antioxidants lead to oxidative stress. A variety of deleterious effects within the lungs are induced by enhanced levels of ROS and lead to pathophysiological conditions such as COPD and asthma.<sup>11–13</sup> Moreover, findings in studies using the canine lung or bovine trachea as models have determined that contractions of smooth muscle can be triggered by hydrogen peroxide and increased levels of environmental oxygen.<sup>14</sup> Enhanced ROS levels have been shown to impair cellular functions and enhance inflammatory reactions mediated through damage-inducing carbohydrates, proteins, lipids, and DNA. These cells are stimulated by various factors leading to the activation of the membrane-bound NADPH oxidase (Nox) complex and the generation of superoxide anion when encountering microorganisms, inhaled particles, or other mediators.<sup>10</sup> Nox-derived ROS can specifically and reversibly alter the half-life, localization, and activity of proteins. The role of the Nox/ROS pathway is associated with the regulation of cellular signaling.<sup>15</sup> Moreover, in the airway alveolar epithelium, ROS have been shown to induce the expression of inflammatory mediators, such as interleukin (IL)-6, tumor necrosis factor (TNF)- $\alpha$ , and IL-1 $\beta$ .<sup>16</sup> Several studies have indicated that oxidants can promote inflammation via the upregulation of transcription factors such as nuclear factor-kappaB (NF- $\kappa$ B) and activator protein 1 (AP-1), which are redox-sensitive and orchestrate the expression of multiple inflammatory genes recognized to be implicated in COPD, such as TNF- $\alpha$ , intercellular

adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), matrix metalloproteinase 9 (MMP-9), cyclooxygenase-2 (COX-2), and cytosolic phospholipases A<sub>2</sub> (cPLA<sub>2</sub>).<sup>17</sup> Therefore, ROS play a crucial role during COPD and asthma attacks. Heme oxygenase-1 (HO-1), also known as heat shock protein 32, is a member of the heat-shock family of proteins that protect against oxidative stress and inflammation. HO-1 quenches ROS by the following mechanisms. Heme is catalyzed by HO-1 to iron, carbon monoxide (CO), and biliverdin-IX $\alpha$ .<sup>18</sup> Biliverdin-IX $\alpha$  is converted to a potent endogenous antioxidant known as bilirubin-IX $\alpha$ , with the function of anti-inflammation,<sup>19</sup> while the iron is sequestered by ferritin, leading to additional anti-apoptotic<sup>19</sup> and antioxidant<sup>20</sup> effects. CO has abundant biological roles, besides its anti-inflammatory activity,<sup>21</sup> and it also shares similar effects of nitric oxide (NO), such as modulation of the vascular tone by increasing cGMP levels and inhibition of smooth muscle cell proliferation and platelet aggregation.<sup>19</sup>

## Mitogen-Activated Protein Kinases (MAPKs) Involved in Pulmonary Inflammatory Diseases

MAPKs are important signaling modules activated by neurotransmitters, growth factors, cytokines as well as mechanical and chemical stressors. Three classes of MAPKs have been identified in mammals: the p38 MAPK, the c-Jun NH2-terminal kinases (JNKs), and the extracellular signal-regulated kinases (ERKs). Asthmatic patients demonstrated increased levels of phospho (p)-JNK1/2, p-p38 MAPK, and p-ERK1/2 in smooth muscle cells or the airway epithelium.<sup>22</sup> The pathogenesis of COPD also appears to be associated with the activation of MAPK pathways.<sup>23</sup> These activated MAPK signals modify both smooth muscle contraction in acute responses and airway structures in chronic conditions.<sup>24,25</sup> In bronchial asthma, MAPKs may control airway remodeling and inflammation.<sup>26</sup> In a paraquat-induced mouse model of acute lung injury (ALI), the p38 MAPK signaling pathway was shown to be an important regulator of TNF- $\alpha$  and IL-1 $\beta$  production, and treatment with the p38 MAPK inhibitor SB203580 improved mortality and pathological scores.<sup>27</sup> A transgenic mouse model developed to overexpress transforming growth factor (TGF)- $\alpha$  in the lung epithelium showed that treatment with a specific MEK inhibitor, ARRY-142886,

prevented the progression of pulmonary fibrosis.<sup>28</sup> Another mouse model of pulmonary fibrosis using house dust mite (HDM) demonstrated that CC-930, a JNK1/2 inhibitor, had a protective effect on lung collagen deposition causing inhibition of pulmonary fibrosis.<sup>29</sup> In addition, our studies in A549 cells and human airway smooth muscle cells, also found that IL-1 $\beta$  or lipoteichoic acid (LTA) could induce MMP-9, COX-2, or cPLA<sub>2</sub> mediated by MAPKs.<sup>30,31</sup> Therefore, MAPKs are important in mediating inflammatory responses in the lung and airway. Several lines of evidence have shown that several agents including herbal ingredients can target MAPKs, these include peroxisome proliferator-activated receptor (PPAR)- $\alpha$  agonists (ciprofibrate,<sup>32</sup> fenofibrate,<sup>33</sup> WY14,643<sup>34</sup>), PPAR- $\gamma$  agonists (rosiglitazone,<sup>35</sup> pioglitazone,<sup>36</sup> LPSF/GQ-2<sup>37</sup>), statins,<sup>38,39</sup> and herb-derived substances (salvianolic acid B,<sup>40</sup> asiatic acid,<sup>41</sup> celastrol,<sup>42</sup> fisetin,<sup>43</sup> galangin,<sup>44</sup> kaempferol,<sup>45</sup> luteolin,<sup>46</sup> madecassoside,<sup>47</sup> oleanolic acid,<sup>48</sup> and pristimerin<sup>49</sup>). We focused on these agents to discuss the molecular mechanisms involved in their activities in the following sections.

## Roles of NF- $\kappa$ B and AP-1 in Pulmonary Inflammatory Diseases

NF- $\kappa$ B has been recognized as an important regulator of inflammatory responses due to its importance in mediating the evolution of inflammation. NF- $\kappa$ B controls a wide spectrum of biological effects including tissue remodeling, tumorigenesis, differentiation, apoptosis, and proliferation, in response to immune and stress insults.<sup>13</sup> While cells are at rest, NF- $\kappa$ B is bound to inhibitory  $\kappa$ B (I $\kappa$ B) an inhibitor protein in the cytoplasm which masks the nuclear translocation signal and thus prevents NF- $\kappa$ B from nuclear translocation. Upon stimulation with various inducers of NF- $\kappa$ B, including several extracellular stimuli, such as oxidative stress, viruses, and environmental particulates [particulate matter (PM10)], TNF- $\alpha$ , and IL-1 $\beta$ , two serine residues of I $\kappa$ B $\alpha$  are rapidly phosphorylated, which target the inhibitor protein for subsequent ubiquitination and degradation, by the E3 ubiquitin-ligases (E3RSI $\kappa$ B, also named  $\beta$ -transducin repeat-containing protein) and the 26S proteasome.<sup>50</sup> The NF- $\kappa$ B dimers are released, as either hetero- or homo-dimers, and translocate into the nucleus where they bind to specific DNA elements and  $\kappa$ B enhancers to activate target genes. ROS have been known to induce the release of cytokines and chemokines such as IL-6, IL-8, TNF- $\alpha$ , IL-1 $\beta$ , and IL-2 and cause ALI in vivo via the activation of

NF- $\kappa$ B.<sup>51</sup> Thus, targeting NF- $\kappa$ B could be a potential strategy in the management of lung injury. A growing number of studies have proven that agents having NF- $\kappa$ B inhibitory activity can block lung inflammation in in vivo models. For example, treatment with emodin effectively prevents E-selectin expression, pulmonary edema, monocyte chemoattractant protein-1 (MCP-1) expression, and pulmonary inflammation in a mouse model of lung injury induced by lipopolysaccharides (LPS) and the inactivation of NF- $\kappa$ B may be the major mechanism involved in these effects.<sup>52</sup> In the LPS-induced ALI model, NF- $\kappa$ B knockdown using intratracheal instillation of small interfering RNA (siRNA) targeting NF- $\kappa$ B p65 also exerts anti-inflammatory effects, which may be due, in part, to the reduction in the levels of the proinflammatory cytokine TNF- $\alpha$ .<sup>53</sup> The upregulation of cytokines is mostly mediated through NF- $\kappa$ B activation. Further, several lines of evidence indicate that lung inflammatory diseases are linked with transcription factor NF- $\kappa$ B activity,<sup>54</sup> by alternatively activating macrophages and regulatory T cells, resulting in the generation and maintenance of a pro-inflammatory environment.<sup>55</sup> In addition, COPD patients express significantly higher amounts of mRNA of NF- $\kappa$ B family genes and elevated levels of inflammatory molecules, IL-1 $\beta$ , IL-8, and COX-2, than those of healthy controls.<sup>56</sup> Clinical evidence has also shown that the severity of COPD is associated with increased NF- $\kappa$ B expression in the epithelia.<sup>57</sup> Furthermore, our previous studies also demonstrated that overexpression of HO-1 can downregulate tumor necrosis factor receptor 1 (TNFR1)-dependent oxidative stress and NF- $\kappa$ B activation to protect against TNF- $\alpha$ -mediated airway inflammation.<sup>58</sup> Thus, in airway inflammation and lung injury, the expression of inflammatory proteins is mediated through NF- $\kappa$ B signaling, which can be a potential target in managing pulmonary inflammatory disorders such as asthma and COPD.<sup>59,60</sup>

Fos (c-Fos, Fos B, Fra-1, Fra-2) and Jun (c-Jun, Jun B, Jun D) family members are subunits of the AP-1 transcription factor and are typically responsible for the transcriptional activation of various genes via binding to the promoters of target genes.<sup>61</sup> For DNA binding, the “leucine zipper” domain of fos-jun or jun-jun dimers is required to regulate the expression of a wide variety of genes.<sup>62</sup> AP-1 binding sites exist in the promoter region of many genes related to inflammatory responses, especially in the promoter region encoding cytokines and chemokines. AP-1 may be activated by various cytokines, including IL-1 $\beta$  and TNF- $\alpha$  via several types of MAPKs and protein kinase C (PKC), which in turn can activate a cascade of intracellular kinases.<sup>61</sup> Thus, many inflammatory mediators can be

transcriptionally regulated by AP-1. In the lungs of smokers, AP-1 and its components c-fos and c-jun are upregulated.<sup>63</sup> Increased AP-1 activities in lung tissues were detected after initiation of the inflammatory response, which was demonstrated by up-regulating mRNAs and proteins of c-jun, jun-B, jun-D, and c-fos, in whole lung tissues and alveolar macrophages.<sup>64</sup> Moreover, in a rat lung fibrosis model induced by intratracheal administration of bleomycin, alveolar macrophages and type II pneumocytes expressed high levels of c-jun and c-fos.<sup>65</sup> Thus, AP-1 has a critical effect on mediating pulmonary inflammatory responses in lung disorders. Moreover, there is growing evidence indicating that in asthmatic airways, a specific inflammatory response may be triggered by the cooperative interaction of these transcription factors (eg NF- $\kappa$ B and AP-1) leading to the optimal expression of specific genes.<sup>66</sup> Thus, in addition to NF- $\kappa$ B, in respiratory diseases, AP-1 is also an important factor.

## Roles of Cytokines and Endotoxins in Pulmonary Inflammatory Diseases

In many diseases, chronic inflammation is an important component of pathogenesis. In the orchestration of chronic inflammation, cytokines exert a critical role in many diseases. Multiple chemokines and cytokines have been implicated in the pathophysiology of asthma and COPD. For example, in asthma, TNF- $\alpha$  has been shown to be highly expressed in the airways, and asthmatic inflammation may be amplified by TNF- $\alpha$ -mediated activation of transcription factors such as NF- $\kappa$ B and AP-1.<sup>67</sup> A high level of TNF- $\alpha$  has also been shown in COPD patients.<sup>68</sup> In asthmatic airways, TNF- $\alpha$  contributes to the dysregulation of inflammatory responses of patients with asthma and COPD who demonstrated increased TNF- $\alpha$  mRNA<sup>69</sup> and protein levels.<sup>68,70</sup> Moreover, when normal subjects were treated with inhaled recombinant TNF- $\alpha$ , they developed airway neutrophilia and airway hyper-responsiveness.<sup>71</sup> However, the detailed mechanisms underlying these observations have not been fully clarified. These responses could be caused by either a direct effect of TNF- $\alpha$  on airway smooth muscle<sup>72</sup> or the release of cysteinyl-leukotrienes LTC<sub>4</sub> and LTD<sub>4</sub>.<sup>73</sup> In asthma patients, mast cells of the airways release mediators that have been suggested to be involved in the pathogenesis of bronchoconstriction and airway hyper-responsiveness.<sup>74</sup> In addition, bacterial infections are involved in several lung and airway inflammatory diseases. The characteristics of these

diseases include pathogen-evoked inflammatory responses in the host. These phenomena have been well validated for LTA in gram-positive bacteria and LPS of gram-negative bacteria.<sup>75</sup> The LPS of gram-negative bacteria and the LTA of gram-positive bacteria are considered to have analogous characteristics in both physiological and biochemical properties.<sup>75</sup> LTA, like LPS, is an amphiphile that is formed by linking a glycolipid to a hydrophilic polyphosphate polymer.<sup>75</sup> Highly purified preparations of LTA from *Staphylococcus aureus* have been used to efficiently activate monocytes via Toll-like receptor 2 (TLR2) to produce TNF- $\alpha$ .<sup>76</sup> LTA is an antigen characterized by inflammatory changes in the lungs exacerbating the severity of respiratory disorders. The inflammatory response is thought to be triggered by the shedding of the epithelial barriers that allow LTA to have relatively easy access to the tracheal smooth muscle cells (TSMCs). Airway inflammation can be due to the expression of a variety of inflammatory proteins in airway smooth muscle, such as IL-6, PLA<sub>2</sub>, COX-2, VCAM-1, and ICAM-1. LTA and TNF- $\alpha$  have been indicated to regulate inflammatory responses by inducing the expression of these inflammatory proteins.

## Roles of Heme Oxygenase-1/Carbon Monoxide in Pulmonary Inflammatory Diseases

Tenhunen et al first identified heme oxygenase (HO) in 1968 when they described the catabolizing of heme.<sup>77</sup> HO has been associated with apoptosis, cell growth, and vascular tone in a variety of pulmonary diseases.<sup>19</sup> The characteristics of the three HO isoforms (HO-1, 2, and 3) have been described previously.<sup>78</sup> HO-1 alone is inducible whereas HO-2 and -3 are constitutively expressed. Although the inducible form, HO-1, is known to be part of the integrated response to oxidative stress and inflammation, only recently has it been linked to the regulation of inflammatory lung disorders.<sup>21</sup> However, we still have not fully understood how HO-1 performs as an anti-inflammatory and cytoprotective protein. HO-1 is expressed in various types of cells, in the lung, including alveolar macrophages and type II pneumocytes, HO-1 is induced by endotoxins, proinflammatory cytokines, NO, heme, hypoxia, or hyperoxia.<sup>19</sup> HO-1 expression is up-regulated, in several pulmonary diseases, including acute respiratory distress syndrome, rejection following lung transplantation,



idiopathic pulmonary fibrosis, COPD, asthma, and cystic fibrosis.<sup>78</sup>

### Asthma

Asthma is an inflammatory disease and presents with limited generalized airflow due to bronchoconstriction. The airways of asthmatic patients feature an accumulation of inflammatory cells and mucus. An imbalance between oxidants and antioxidants contributes to airway inflammation, a key component of asthma, which activates redox-sensitive transcription factors such as AP-1 and NF- $\kappa$ B to upregulate the expression of proinflammatory mediators and cause airway epithelium damage.<sup>66</sup> Accumulating evidence has supported a role for HO-1 in airway inflammation and asthma. Exhaled CO levels were found to be elevated in asthma due to HO-1 induction in alveolar macrophages in most untreated patients experiencing a recent asthmatic attack compared with controls.<sup>18,79</sup> These findings imply that HO-1 exerts a protective role in asthma. Moreover, Almolki et al demonstrated that hemin up-regulates HO-1 to reduce airway responsiveness to histamine, mucus secretion, and airway inflammation in ovalbumin-sensitized guinea pigs.<sup>80</sup> In experiments in mouse models, CO has been found to reduce airway hyperresponsiveness and inflammation.<sup>21</sup> In addition, a recent study also implied that in asthma, the protective effects of HO-1 on airway smooth muscle remodeling were mediated by bilirubin.<sup>19</sup> Recent data have revealed that CO has abundant effects on regulating intracellular signaling processes, which culminate in anti-coagulative, anti-apoptotic, anti-proliferative, and anti-inflammatory effects.<sup>19</sup> Conversely, HO-1 has also been reported to impede cell rolling, adhesion, and migration of immune cells from the vessel, possibly due to its down-regulating abilities on the expression and function of adhesion molecules in the endothelium.<sup>81</sup>

### Chronic Obstructive Pulmonary Disease

COPD is a progressive disorder characterized by irreversible airflow limitation caused by chronic inflammation affecting primarily the lung peripheral airways and parenchyma. In the pathogenesis of COPD-related inflammation, oxidative stress plays a crucial role by activating proinflammatory transcription factors such as NF- $\kappa$ B to secrete a variety of proinflammatory mediators, including growth factors, cytokines, chemokines, and lipid mediators in inflammatory cells and structural cells, including epithelial and endothelial cells and fibroblasts. ROS can oxidize different biomolecules such as lipids, proteins, and DNA

leading to impaired physiological functions including inactivation of antiproteases, which in turn cause epithelial injury and death as well as aging and other diseases. An imbalance between the oxidant/antioxidant status and increased ROS exposure such as through cigarette smoke and chronic infections are risk factors for the development of COPD. Cells and tissues possess endogenous antioxidant defense systems including the tripeptide glutathione (GSH). The HO-1/CO system also acts as another anti-oxidative stress system. Moreover, a reciprocal regulation exists between GSH concentration and HO-1. HO-1 is transcriptionally upregulated by depletion of GSH.<sup>82</sup> A previous study found that alveolar macrophages isolated from bronchoalveolar fluid (BALF) in patients with COPD have reduced levels of HO-1 expression.<sup>83</sup> Furthermore, humans express two potentially functional polymorphisms in the HO-1 gene promoter region, which induce different HO-1 transcriptional responses. Polymorphisms of the HO-1 promoter associated with a strong ability to induce HO-1 expression may be an important endogenous protective factor to reduce susceptibility to COPD.<sup>84</sup> Moreover, HO-1 induction may attenuate senescence, including reduced replicative capacity, and the inflammatory profile in fibroblasts isolated from COPD patients by restoring mitophagy and protecting against mitochondrial dysfunction.<sup>85</sup> In a rat model of smoke-induced emphysema, injection with protoporphyrin IX upregulated HO-1, which in turn attenuated the development of smoke-induced emphysema, the levels of inflammatory mediators, inflammatory cell infiltration as well as oxidative damage.<sup>86</sup> Thus, upregulation of HO-1 may possibly decrease the susceptibility of developing COPD.

The clinical significance of HO-1 expression during asthma is still an open issue. HO-1 or its products may be beneficial as both therapeutic and diagnostic targets. Defining not only the regulation of HO-1 during lung and airway inflammation but also the diagnostic and therapeutic roles of the HO-1 pathway in COPD and asthma will remain an important avenue of research in the near future. Below we will discuss the protective mechanisms of HO-1/CO in respiratory inflammatory diseases. We particularly focus on herbal medicines with the potential to induce HO-1 expression, including salvianolic acid A,<sup>87</sup> asiatic acid,<sup>41</sup> celastrol,<sup>88</sup> fisetin,<sup>89</sup> galangin,<sup>90,91</sup> kaempferol,<sup>92–95</sup> luteolin,<sup>96</sup> madecassoside,<sup>97,98</sup> oleanolic acid,<sup>99,100</sup> saikosaponin A,<sup>101</sup> 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO),<sup>102</sup> and pristimerin.<sup>49,103</sup> In the following

sections, the detailed pharmacological mechanisms of these herb ingredients will be further discussed.

## Redox-Dependent Transcription Factors Mediate Inducible HO-1 Gene Expression

Cytokines, oxidative stress signals, growth factors, and bacterial compounds, can all act as inducers of HO-1 expression in different species. In particular, HO-1 is regulated at the transcriptional level and the HO-1 promoter contains multiple cis-acting regulatory elements, which have been shown to control basal and inducible HO-1 gene expression.<sup>19,104,105</sup> E1 and E2 (two upstream enhancers regulating HO-1 induction) are located in the upstream enhancer regions, which play key roles for the redox-dependent induction of HO-1.<sup>105</sup> Several antioxidant response elements (AREs) have been found to exist in both E1 and E2 enhancer regions, as well as in the promoter regions of other stress-inducible antioxidant and Phase 2 detoxifying genes.<sup>106,107</sup> The GT-microsatellite polymorphism localized in the proximal human HO-1 gene promoter region is an important difference between the rodent and human HO-1 genes having major biological relevance. In response to stress stimuli, a lower number of GT repeats within this polymorphic sequence leads to higher inducibility of the HO-1 gene<sup>108</sup> and this allele seems to be associated with protective ability against cardiovascular disorders.<sup>84</sup> Below, we will discuss the critical role of the NF-E2-related factor 2 (Nrf2) a major redox-dependent transcription factor in regulating inducible HO-1 gene expression by statins, PPAR agonists, and Chinese herbal medicines in pulmonary resident cells.

## Nrf2 Signaling in Coordinated Activation of Antioxidant Gene Expression

Electrophiles and oxidants impose persistent stresses and exacerbate many chronic diseases. For example, aging and age-related diseases, such as chronic inflammation, cancer, neurodegenerative diseases, and cardiovascular disease are induced by oxidative stresses. In these processes, oxidative stress increases the levels of oxidized DNA, phospholipids, and proteins. At the same time, cells have developed adaptive mechanisms to dynamically offset intrinsic and extrinsic electrophile and oxidant levels imposed by environmental stresses. These systems involve four categories of mechanisms: (1) redox reactions often catalyzed by cytochrome p-450 enzymes, through functional groups

that are exposed or introduced onto largely hydrophobic organic molecules; (2) efflux transporters that export toxic metabolites; (3) nucleophilic trapping processes that engage cellular nucleophiles or GSH and electrophilic xenobiotics to facilitate excretion, such as conjugations of cofactors containing electrophilic adenosine with nucleophilic xenobiotics and those catalyzed by GSH *S*-transferases (GSTs), as well as enzymes, such as catalase,<sup>109</sup> GSH peroxidase, and, superoxide dismutases (SOD) which detoxify ROS; and (4) intracellular GSH and thioredoxin, which contain thiol-molecules to maintain reducing conditions. When a cell encounters a potentially toxic agent, the outcome is often largely determined by the balance between reactive intermediates activated by the activities of enzymes from substrates, and these reactive species are detoxified by enzymatic activities. At least three essential components are required to induce this protective response: (a) Nrf2, the transcription factor binds to the ARE through heterodimerization with members of the small Maf family of transcription factors, and expresses ARE-regulated genes by recruiting the general transcriptional machinery; (b) AREs, present on each gene in either single or multiple copies, are upstream regulatory sequences; and (c) Kelch-like ECH-associated protein 1 (Keap1), a repressor protein located in the cytosolic compartment binds to Nrf2, sequesters it in the cytoplasm and thus allows its degradation via the proteasome-ubiquitin protein degradation pathway. For stress signals, several critical cysteine residues on Keap1 serve as primary sensors and conformational changes on Keap1, which are modified by these oxidative stresses, thereby leading to the release of Nrf2. In addition, the detoxification of xenobiotics via conjugation and trapping processes catalyzed by the classical environmental stress response, and genomic analyses indicate that this transcription factor induces gene families to provide antioxidative and anti-inflammatory reactions.

## HO-1 Inducers

### Pharmacological Induction of HO-1 as an Anti-Inflammatory Therapeutic Target

Cobalt protoporphyrin IX, commonly used in *in vitro* experimental cell models and animal models, is a type of metalloporphyrin and the prototypical inducer of HO-1. Metalloporphyrins are severely toxic and lack cell specificity and are not suitable for clinical interventions. Similarly, heme has been approved for the

treatment of acute intermittent porphyria (heme arginate), which is one of the most potent inducers of HO-1 and only has limited potential for the management of inflammation. A growing body of literature has indicated that HO-1 induction can exert protective effects via decreasing inflammation, apoptosis, vascular remodeling, fibrosis, and improving survival rate in lung injury models including COPD, asthma, pulmonary hypertension, adult respiratory distress syndrome, and pulmonary fibrosis.<sup>21,78</sup> In contrast, several pharmacological compounds are currently available, which act as HO-1 inducers and are used in standard therapies, and might also be effective for the clinical intervention of inflammatory disorders. For example, statins, with cholesterol-lowering effects, were initially introduced for the prevention of arteriosclerosis but have also been recognized to induce HO-1 and to exhibit anti-inflammatory effects.<sup>110,111</sup> HO-1 induced by protoporphyrin IX can attenuate the development of smoke-triggered emphysema mediated through anti-inflammatory and antioxidant effects.<sup>86</sup> Our recent studies have demonstrated that HO-1 is induced by mevastatin mediated via a Nox/ROS-dependent c-Src/PDGFR $\alpha$ /PI3K/Akt/Nrf2/ARE cascade or via c-Jun activation of PKC $\alpha$ /Pyk2/p38 $\alpha$  MAPK or JNK1/2 to suppress proinflammatory mediators-mediated inflammatory responses in human pulmonary alveolar epithelial cells (HPAEPiCs).<sup>112,113</sup> Carbon monoxide-releasing molecule (CORM-2) induces HO-1 expression via Src, epidermal growth factor receptor (EGFR), and PI3K/Akt to increase the formation of the Nrf2 and AREs complex in HPAEPiCs to suppress TNF- $\alpha$ -mediated inflammatory responses.<sup>114</sup> CORM-2 also activates a PYK2/PKC $\alpha$ /ERK1/2/AP-1 pathway leading to HO-1 expression in HPAEPiCs.<sup>115</sup> We determined that CORM-2-induced HO-1 expression in human tracheal smooth muscle cells (HTSMCs) was mediated through the PKC $\alpha$ /Pyk2-dependent Nox/ROS/ERK1/2/AP-1 pathway, which can mitigate lipopolysaccharide-induced airway inflammation.<sup>116</sup> CORM-2 also activates the c-Src/EGFR/PI3K/Akt/JNK1/2 and p38 MAPK pathways, which in turn trigger Nrf2 activation to induce HO-1 expression in HTSMCs.<sup>117</sup> Interestingly, our previous data also demonstrated that the particle-phase extract of cigarette smoke can activate Nrf2 to induce HO-1 expression via a c-Src/NADPH oxidase/ROS/MAPK pathway in HTSMCs.<sup>118</sup> Below, we will review the

pharmacological effects of HO-1 expression in protecting against lung inflammation.

A novel therapeutic approach for treating oxidative stress and inflammation involves agonists of PPAR, which were originally used as antidiabetic and dyslipidemia agents. The anti-inflammatory effects of PPAR agonists likely account for these protective roles in these diseases. The capability of PPAR agonists to repress proinflammatory genes is exerted via the antagonism of transcription factors including signal transducer and activator of transcription (STAT), AP-1, ATF-1 and 4, and NF- $\kappa$ B.<sup>119</sup> In mixed neuron-glia cultures, PPAR agonists have been demonstrated to impede the transcription of the inducible form of nitric oxide synthase<sup>120</sup> and COX-2.<sup>121</sup> In addition, PPAR agonists possess anti-oxidative and anti-inflammatory effects through the induction of HO-1.<sup>122</sup>

Natural herbs and herbal supplements can exert extensive health benefits. Based on traditional Chinese herbal medicines, herbs have been used as far as the first century CE or earlier. Indeed, herbs have a variety of functions including medicinal, culinary, and spiritual in some cases. With regard to medicine, herbs exert a wide range of pharmacological effects including anti-oxidative and anti-inflammatory activities. We will focus on the potential effectiveness of several pure compounds extracted from traditional Chinese herbal medicines.

Due to the immunomodulatory actions of HO-1 in various types of cells, these traditional Chinese herbs might be specifically applicable to HO-1 induction in pulmonary resident cells as medicinal interventions. Significant anti-oxidative and anti-inflammatory therapeutic effects have been described by HO-1 induction in these cells. Therefore, we will characterize and identify the pharmacological mechanisms that upregulate HO-1 expression in various resident cells of the pulmonary system based on in vivo and in vitro studies.

PPARs, ligand-inducible transcription factors, belong to a superfamily of the nuclear receptor superfamily. To date, three PPAR isotypes, encoded by separate genes, including PPAR- $\alpha$ , PPAR- $\beta/\delta$ , and PPAR- $\gamma$ , have been identified.<sup>123</sup> PPARs mainly control inflammation, lipid metabolism, adipogenesis, and the maintenance of metabolic homeostasis through the regulation of the expression of related gene networks. Three PPAR isoforms are activated by fatty acid-derived eicosanoids and fatty

acids. They act as lipid sensors that can regulate metabolism. A distinct tissue distribution pattern exists among these three PPAR isotypes, in the regulation of energy metabolism and their associated functions. PPAR- $\alpha$  is expressed in tissues including muscles, kidney, heart, and liver, and mainly regulates the metabolism of lipoproteins and lipids mediated through the regulation of target gene expression.<sup>124</sup> Except in the liver, PPAR- $\beta/\delta$  is expressed in all body tissues.<sup>124</sup> In skeletal muscle, adipose tissue, and the heart, PPAR- $\gamma$  has emerged as an important regulator of energy balance and lipid metabolism.<sup>125</sup> The PPAR- $\gamma$  protein exists in two isoforms obtained by utilizing distinct 5'-exons and promoters expressed from the same gene sequence. Compared to PPAR- $\gamma$ 1, PPAR- $\gamma$ 2 exerts higher transcriptional activity, which is determined by the ligand-independent domain at the N-terminal end and by an additional stretch of 30 amino acid residues.<sup>126,127</sup> The distribution pattern of these two PPAR- $\gamma$  isoforms is distinct. PPAR- $\gamma$ 1 is mainly expressed in hematopoietic cells, the large intestine, and in adipose tissue and to a lower extent in the small intestine, liver, muscles, pancreas, and kidney. Under physiological conditions, PPAR- $\gamma$ 2 is restricted to brown and white adipose tissue.<sup>124,128</sup> All three PPAR subtypes share an identical gene transcription process. PPARs form heterodimers with the retinoid X receptor (RXR), another ligand-activated nuclear receptor, for ligand binding. The PPAR-RXR heterodimer binds to peroxisome proliferator response elements (PPREs), which are DNA-specific sequences in the promoter area of specific target genes.<sup>129</sup> When different transcriptional cofactors are recruited, the transcription process is started.<sup>130</sup> In addition to differential distribution patterns, PPAR isoforms possess distinct sensitivities and selectivity to ligands and vary in the recruitment of different coactivator proteins, which result in the regulation of different sets of target genes. PPAR- $\alpha$  generally regulates genes implicated in inflammation, vascular function, fatty acid uptake, and oxidation; whereas, PPAR- $\gamma$  regulates genes implicated in inflammation, glucose homeostasis, and fatty acid uptake and storage. PPAR- $\delta$  regulates genes implicated in macrophage lipid homeostasis, inflammation, and fatty acid metabolism.<sup>131</sup>

PPAR agonists are used for the treatment of metabolic syndrome and cardiovascular disease (CVD). However, during recent decades, PPAR- $\alpha$  and PPAR- $\gamma$  have been implicated in the regulation of inflammation, including lung inflammation. We will discuss the recent

evidence supporting the effects of PPAR- $\alpha$  and PPAR- $\gamma$  against inflammatory response and define potential targets as a novel strategy for the management of pulmonary inflammation. PPARs are triggered by both synthetic and natural ligands, which are either non-selective or isotype-selective. A variety of endogenous fatty acids have been identified as the main ligands for PPAR- $\alpha$ , such as the arachidonic acid derivative leukotriene B<sub>4</sub> (LTB<sub>4</sub>) and 8S-hydroxyeicosatetraenoic acid. Dehydroepiandrosterone, a precursor of both estrogens and androgens, and oleoyl ethanolamide, a regulator of body mass and feeding, are other activators of PPAR- $\alpha$  activity derived from natural sources. Other compounds such as fibrates are synthetic molecules used clinically to treat dyslipidemia and include bezafibrate, ciprofibrate, and fenofibrate, as well as GW2331 and Wy-14,643, also act as pharmacological tools in inflammatory studies.

The main PPAR- $\gamma$  agonists include endogenous ligands, such as the 12/15 lipoxygenase products 13-hydroxyoctadecadienoic acid and 15-hydroxyeicosatetraenoic acid, and the cyclopentenone prostaglandin 15-deoxy-D12,14-prostaglandin J<sub>2</sub> (15d-PGJ<sub>2</sub>), as well as thiazolidinediones (TZDs) belonging to the synthetic compounds used in the clinic for their antidiabetic effects. Our recent studies have indicated that HO-1 expression induced by rosiglitazone is mediated through PKC $\alpha$ /AMPK $\alpha$ /p38 MAPK $\alpha$ /Sirtuin 1 (SIRT1)-dependent deacetylation of Ac-PGC1 $\alpha$  and fragmentation of nuclear receptor corepressor (NCoR)/PPAR- $\gamma$  activation in HPAEpiCs, which protects against the inflammatory responses triggered by LPS.<sup>132</sup> Moreover, we also found that rosiglitazone induced-HO-1 expression can be mediated through either NOX/ROS/c-Src/Pyk2/Akt-dependent Nrf2 activation or via PPAR- $\gamma$  in HPAEpiCs to mitigate LPS-mediated inflammatory responses.<sup>122</sup> Ibuprofen and indomethacin are non-steroidal anti-inflammatory drugs that also activate PPAR- $\gamma$  when used at higher concentrations than those required to attenuate the activity of cyclooxygenase enzyme.<sup>133</sup> Among these compounds, 15d-PGJ<sub>2</sub> has been widely applied to evaluate the potential effects of PPAR- $\gamma$  as a mediator of anti-inflammatory activity. However, it must be indicated that 15d-PGJ<sub>2</sub> at micromolar concentrations also activates PPAR- $\alpha$ , although it is considered a selective agonist of PPAR- $\gamma$ . Furthermore, many studies have provided evidence that 15d-PGJ<sub>2</sub> may also regulate PPAR- $\gamma$ -dependent anti-inflammatory activity in the lungs.



## Roles of PPARs in Pulmonary Inflammatory Diseases

Among the PPARs, PPAR- $\alpha$  was the first shown to have a role in the control of inflammation.<sup>134</sup> Devchand et al (1996) found that direct interaction between LTB<sub>4</sub> and PPAR- $\alpha$  increased the catabolism of LTB<sub>4</sub> and induced enzymes involved in fatty acid degradation, which further enhanced PPAR- $\alpha$  function by either increasing receptor levels or activating the receptor. Several studies using PPAR agonists in knock-out mice or wild-type animals, as well as clinical trials in human, have provided evidence for the anti-inflammatory properties of PPAR- $\gamma$  and PPAR- $\alpha$  in various diseases including atherosclerosis,<sup>135–139</sup> inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease;<sup>140–142</sup> myocardial infarction and stroke;<sup>133,143</sup> rheumatoid arthritis,<sup>144–146</sup> psoriasis,<sup>147,148</sup> COPD;<sup>149</sup> and allergic dermatitis.<sup>150,151</sup>

### PPAR- $\gamma$ Agonists: Rosiglitazone

Hammad et al, using ovalbumin (OVA)-pulsed dendritic cells transfer into the intratracheal region as a sensitization model, showed that rosiglitazone, a selective PPAR- $\gamma$  agonist, prevents eosinophilic airway inflammation by draining mediastinal lymph nodes, reducing Ag-specific T cell proliferation, and by increasing IL-10 levels produced by T cells.<sup>152</sup> Another study exploring the pathogenesis of asthma also revealed that the protective role of rosiglitazone is partly mediated through a mechanism dependent on IL-10.<sup>153</sup> Intranasal administration of rosiglitazone significantly blocked not only airway smooth muscle remodeling and the eosinophilic inflammatory response in mice models of eosinophilic airway inflammation following exposure to OVA, but rosiglitazone also decreased the expression of NF- $\kappa$ B and TLR-4 in the OVA-exposed group.<sup>154</sup> Similarly, in a 1% cigarette smoke extract in vitro model, rosiglitazone also down-regulated the expression of NF- $\kappa$ B and TLR-4 in 16HBE cells (bronchial epithelial cells).<sup>155</sup> The inhibition of the NF- $\kappa$ B pathway by rosiglitazone treatment also attenuated airway mucus hypersecretion and the inflammatory response induced by acrolein in rats.<sup>156</sup> Furthermore, rosiglitazone treatment also attenuated ROS production by reducing myeloperoxidase<sup>157</sup> activity<sup>157</sup> and expression of ICAM-1, and pulmonary overproduction of cytokine-induced neutrophil chemoattractant-1 (CINC-1) and

TNF- $\alpha$  as well as malondialdehyde (MDA) levels via blocking the nuclear translocation of NF- $\kappa$ B in an endotoxemia rat model.<sup>158</sup>

In a microparticle (MP) in vitro model using human lung epithelial cells and A549 alveolar cells, pre-incubation with 15-deoxy-D12,14-prostaglandin-J<sub>2</sub> and rosiglitazone reduced NF- $\kappa$ B activation and the synthesis of MCP-1 and IL-8,<sup>159</sup> the effects of rosiglitazone were reversed by GW9662, the specific PPAR- $\gamma$  antagonist. Momoi et al also demonstrated similar findings in A549 cells, whereby thiazolidinedione inhibited IL-1 $\alpha$  and TNF- $\alpha$  induced endogenous MCP-1 messenger RNA expression and protein secretion.<sup>160</sup> The effects of rosiglitazone on inhibition of NF- $\kappa$ B were also indicated by Cheng et al who revealed that the PPAR- $\gamma$  agonist rosiglitazone inhibited NF- $\kappa$ B expression to ameliorate airway inflammation in asthmatic mice, leading to inhibition of inflammatory corpuscle activity of TLR2/Nod-like receptor with pyrin domain containing 3 (NLRP3).<sup>161</sup> In the progression of respiratory diseases, such as COPD, neutrophils are important inflammatory cells. In the LPS-induced acute porcine lung injury model,<sup>78</sup> intravenous rosiglitazone significantly controlled local pulmonary inflammation as reflected by a significant reduction in the expression of cytokines and neutrophil activity within the alveolar compartments.<sup>162</sup>

Other studies have demonstrated that when rosiglitazone is used after or before exposure to the aerosolized LPS insult, which induces neutrophilia and associated survival factors/chemoattractants such as CC chemokine ligand-5 (CCL5) and granulocyte colony-stimulating factor (G-CSF) in the airways, it inhibits airway inflammation.<sup>163–166</sup> In addition, several lines of evidence have found that rosiglitazone achieves its anti-inflammatory effects through the upregulation of HO-1 expression.<sup>122,132,167,168</sup> Many PPAR- $\gamma$  ligands modulate multiple cellular pathways via both PPAR- $\gamma$ -dependent and independent pathways, thus for human diseases including lung disease, these ligands are under evaluation as potential remedies.<sup>169</sup> Our recent studies have demonstrated that HO-1 is up-regulated via PPAR-dependent and independent pathways,<sup>122,132</sup> and attenuates the LPS-induced inflammatory responses in pulmonary resident cells. Kadam et al also revealed that rosiglitazone treatment significantly elevates the expression of Nrf2 and HO-1, which have a lower expression in macrophages from the animals treated with LPS.<sup>170</sup>

Rosiglitazone ameliorated the lung injury in a mouse model of ALI and promoted epithelial sodium channel (ENaC)-mediated alveolar fluid clearance (AFC) to alleviate pulmonary edema via PPAR- $\gamma$ /serum and glucocorticoid-induced kinase-1 (SGK1) signaling pathway dependence.<sup>171</sup>

Based on the literature, rosiglitazone inhibits inflammation-related lung remodeling. Rosiglitazone reduced the levels of MMP-9 and MMP-2 proteins by attenuating MAPKs and NF- $\kappa$ B activation in lung tissues of COPD rat models.<sup>35</sup> Rosiglitazone treatment inhibits lung fibroblasts stimulated by fetal bovine serum (FBS) and growth factor proliferation, migration, and myofibroblast transdifferentiation in vitro, suggesting that PPAR- $\gamma$  agonists may rescue pulmonary fibrosis.<sup>172</sup> Another pulmonary fibrosis murine model induced by bleomycin also demonstrated the therapeutic activity exerted by rosiglitazone in pulmonary fibrosis based on findings revealing normal lung features on micro-computed tomography (CT) scans were achieved in the majority (80%) of the intervention group.<sup>173</sup> Interestingly, Ward et al found that in a murine model of allergen-induced inflammation, rosiglitazone reduces airway hyperresponsiveness, which is potentially mediated through an anti-inflammatory action-independent effect.<sup>174</sup> These studies have revealed that rosiglitazone possesses a broad range of effects in pulmonary inflammatory disorders.

## Other Thiazolidinedione PPAR- $\gamma$ Agonists

Treatment with ciglitazone significantly reduced I $\kappa$ B kinase<sup>175</sup> activity and I $\kappa$ B $\alpha$  degradation and completely inhibited NF- $\kappa$ B DNA binding. This reduction of IKK activity induced by ciglitazone appeared to be a consequence of physical interaction between PPAR- $\gamma$  and IKK. Ciglitazone may ameliorate lung inflammatory injury following hemorrhagic shock, which appears to be mediated by inhibition of the IKK/NF- $\kappa$ B pathway.<sup>176</sup> Pioglitazone ameliorates ALI and following fibrosis induced by bleomycin, at least partly through suppression of the expression of connective tissue growth factor (CTGF), TNF- $\alpha$ , and procollagen I.<sup>177</sup> PPAR- $\gamma$  agonists ciglitazone and troglitazone inhibit myofibroblast differentiation and collagen secretion in human lung fibroblast cells induced by TGF- $\beta$ 1. Thus, in a murine model of bleomycin-induced fibrosis, PPAR- $\gamma$  agonists also inhibit lung fibrosis.<sup>178</sup> The inhibitory effects of pioglitazone, a PPAR- $\gamma$  agonist, on

hyperresponsiveness, airway inflammation,<sup>179</sup> and remodeling were shown to be mediated through the upregulation of regulator of G protein signaling 4 (RGS4) via ERK1/2 and Akt/mammalian target of rapamycin (mTOR) signaling in OVA-induced asthma in BALB/c mice.<sup>36</sup> Similar to rosiglitazone, PPAR- $\gamma$  ligands 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) and 15d-PGJ<sub>2</sub> may promote HO-1 upregulation in a PPAR-independent mechanism and possess potent antifibrotic effects in vitro in primary human lung fibroblasts. CDDO and 15d-PGJ<sub>2</sub> upregulate HO-1 via a GSH-dependent mechanism implicating a complex formation of covalent bonds between CDDO or 15d-PGJ<sub>2</sub> and glutathione (GSH) but does not involve Nrf2 or AP-1 activity.<sup>180</sup>

Like rosiglitazone-induced inhibition of chemotaxis of neutrophils, the PPAR- $\gamma$  ligands troglitazone and 15d-PGJ<sub>2</sub> also inhibit polymorphonuclear leukocytes (PMN) chemotactic responses to N-formyl methionyl-leucylphenylalanine (fMLP) and IL-8 in sepsis patients and mice models of sepsis.<sup>181</sup> The PPAR- $\gamma$  agonist ciglitazone inhibits pro-inflammatory pathways in NIH-A549 cells by blocking the overexpression of nitric oxide synthase (NOS) induced by cytokine and cytokine-induced IL-8 secretion.<sup>182</sup> CDDO, a PPAR- $\gamma$  ligand, is a potent inhibitor of the differentiation of human lung fibroblasts to myofibroblasts stimulated by TGF- $\beta$ , and attenuates the expression of collagen, fibronectin, and  $\alpha$ -smooth muscle actin via a pathway not related to PPAR- $\gamma$ .<sup>183</sup> The PPAR- $\gamma$  ligands 15d-PGJ<sub>2</sub> and troglitazone virtually abrogate Egr-1 activity and target its inflammatory gene in hypoxic mononuclear phagocytes, which provide a potentially protective effect on ischemic pulmonary injury.<sup>184</sup>

In the guinea pig model of acute lung inflammation induced by LPS, pioglitazone is effective in attenuating the dysfunction of the lung by abrogating oxidative stress, TNF $\alpha$  release, and neutrophilia.<sup>185</sup> Synthesis of thiazolidines derivatives-LPSF/GQ-2 anti-inflammatory action of lung injury could be attributed to the inhibition of NF- $\kappa$ B, ERK1/2, p38 MAPK, and poly(ADP-ribose) polymerase (PARP) pathways.<sup>37</sup>

## PPAR- $\alpha$ Agonists

Fenofibrate is a lipid-modifying agent derived from fibric acid, which can activate the PPAR- $\alpha$ . The most common and serious form of idiopathic interstitial pneumonia is idiopathic pulmonary fibrosis. Typical

characteristics include abnormal alveolar structure accompanied by collagen deposition and myofibroblast accumulation in the extracellular matrix. Samah et al revealed that fenofibrate attenuates the severity of lung fibrosis and injury induced by bleomycin by decreasing pulmonary hydroxyproline and TGF- $\beta$ 1 levels as effectively as rosiglitazone.<sup>186</sup> Dexamethasone or fenofibrate attenuates the severity of bronchial asthma and airway inflammation induced by OVA/LPS through significant amelioration in lung inflammatory cytokines such as TNF- $\alpha$ , IL-4, IL-13, IL-17, IL-23, and TGF- $\beta$ 1 levels, in the serum immunoglobulin (Ig)E, and leukocytic counts.<sup>187</sup> In a mouse model, fenofibrate decreased airway reactivity to methacholine in a dose- and time-dependent manner via an enhanced endothelial NOS (eNOS) phosphorylation to upregulate NO generation.<sup>188</sup> Fenofibrate protects fatty acid oxidation-induced alveolar epithelial cells dysfunction, a crucial influencer of the pathogenesis of pulmonary injury.<sup>189</sup> Fenofibrate (15 mg/day) triggered T helper type 1 (Th1) switching in the immune response to allergens by overcoming inflammatory activity in allergic asthma models induced by OVA+LPS.<sup>190</sup> Fenofibrate was shown to mitigate acute pulmonary injury<sup>78</sup> in an intestinal ischemia/reperfusion (I/R) model in mice by decreasing inflammatory factors.<sup>191</sup> Fenofibrate reduced the production of the following neutrophilic chemokines induced by IL-1 $\beta$ : ENA-78, G-CSF, GM-CSF, and TNF- $\alpha$ .<sup>192</sup> Fenofibrate suppressed the down-regulation of PPAR- $\alpha$  associated with airway inflammation in the lung of mice exposed to LPS or OVA.<sup>193</sup> Further, the PPAR- $\alpha$  agonist fenofibrate downregulated chemoattractant production, cell infiltration, and enhanced MMP activity in mouse lung triggered by LPS.<sup>194</sup>

Ciprofibrate inhibited rat airway smooth muscle cell contraction and proliferation induced by cigarette smoke extract in vitro. Ciprofibrate could attenuate airway remodeling in cigarette smoke-exposed rats model of COPD by inhibiting airway hyper-contraction, ameliorating airway smooth muscle proliferation, and reducing IL-1 $\beta$ , IL-12p70, IL-17A, and IL-18 expression.<sup>195</sup> Fenofibrate or ciprofibrate downregulates the binding activity of AP-1 and NF- $\kappa$ B induced by TNF $\alpha$  and protects against VCAM-1 and IL-6 gene expression induced by TNF- $\alpha$  in porcine vascular endothelial cells.<sup>196</sup>

WY14,643, a synthetic fibrate drug, blocks the elevation of the capillary filtration coefficient (K<sub>fc</sub>) in a mice

model of ALI induced by LPS.<sup>197</sup> WY14,643, in a mouse model of ALI induced by LPS, also inhibited the LPS-stimulated induction of nitroxidative stress and pro-inflammatory cytokine levels.<sup>198</sup> Furthermore, WY14643 could also up-regulate TGF- $\beta$ , IL-4, and IL-10 mRNA expression and also attenuated rejection of lung allografts.<sup>199</sup>

## The Role of Statins in Pulmonary Inflammatory Diseases

Statins, also known as 3-hydroxy-3-methyl- glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, were introduced into clinical practice due to their cholesterol-reducing properties and have a proven benefit in the prognosis of ischemic heart disease by lowering the incidence of illnesses and mortality in patients who are at high risk of CVD.<sup>200</sup> A meta-analysis study including a total of 70,388 individuals enrolled in 10 trials found that treatment with statins significantly reduced the risk of major coronary events (odds ratio [OR] 0.70, 95% confidence interval [CI]: 0.61–0.81), major cerebrovascular events (OR 0.81, 95% CI: 0.71–0.93), and all-cause mortality (OR 0.88, 95% CI: 0.81–0.96).<sup>201</sup> In addition, retrospective longitudinal dynamic cohort studies found that statins could decrease exacerbation of COPD by reducing the number of hospitalizations or emergency room and outpatient visits.<sup>202,203</sup> In COPD patients, statins can also reduce pulmonary hypertension, the level of C-reactive protein (CRP), and the risk of mortality, compared with those not taking statins.<sup>204,205</sup> For instance, a review has indicated that COPD patients taking statins have lower cardiovascular and respiratory morbidity/mortality, lower risk of lung cancer, and statins also reverse the decline in forced expiratory volume in one second (FEV1).<sup>206</sup> Another study also showed that COPD patients receiving long-term statins (>2 years) were associated with a 39% reduced risk of mortality, and in particular, a 78% reduced mortality was reported for a subgroup of patients with a high level of systemic inflammation with high-sensitivity CRP (hsCRP) higher than 3 mg/L.<sup>207</sup> Moreover, with regard to the overall survival of patients with non-small-cell lung cancer, statins potentially enhanced the effects of chemotherapy [(hazard ration (HR) 0.86, 95% CI: 0.81–0.91] and of tyrosine kinase inhibitors (HR 0.86, 95% CI: 0.76–0.98).<sup>208</sup> Statins have a beneficial effect on the

overall survival rate of lung cancer patients. Moreover, in COPD patients, statins may have a beneficial effect on decreasing the risk of lung cancer.<sup>209</sup> A study analyzing patient data from 2002 to 2017 from the Taiwan National Health Insurance program indicated that statins may protect COPD patients from pulmonary hypertension (PH) in a dose- and time-dependent manner: Compared with statin nonusers, statin users had a 22% lower risk of PH (subdistribution HR [sHR] 0.78, 95% CI: 0.65–0.94).<sup>210</sup> Moreover, Chalmers et al also revealed that statin users were associated with a significant decrease in the development of complicated pneumonia (adjusted odds ratio [aOR] 0.44, 95% CI, 0.25–0.79,  $P=0.006$ ), lower 30-day mortality [aOR 0.46, 95% CI 0.25–0.85,  $P=0.01$ ], and lower CRP levels on admission.<sup>211</sup> Therefore, statins could be a potential therapy for the management of lung inflammation.

Statins may exert anti-inflammatory properties in the management of COPD. How do statins achieve anti-inflammatory effects in the lung? Statins may attenuate pulmonary inflammation by modulating neutrophil function and infiltration into the lung, by reducing cytokine expression and release, by preserving epithelial and endothelial integrity, by reversing airflow limitation in the lung through inhibiting fibrotic activity, by exerting antioxidant effects on skeletal muscle, by protecting against disruption of pulmonary integrity in community-acquired pneumonia, by reducing the pulmonary infection-mediated lung inflammatory response, and reverse or inhibit the development of epithelial-mesenchymal transition.<sup>205,212</sup> Statins via the mevalonate pathway can affect the development of lung cancer and COPD. The mevalonate pathway mediates important intracellular signaling molecules called guanine phosphate transferases (GTPases) such as Rho-A to achieve these effects. While inhibiting the mevalonate pathway, leading to inhibition of the innate immune response to the inflammatory triggers such as smoking, may play a crucial role in lung remodeling and modifying pulmonary inflammation.<sup>213</sup> Statins may also attenuate Nox activity via inhibition of Rac1 geranylgeranylation, protect the endothelial cell barrier, and regulate both mRNA stability and enzyme activity of eNOS to exert their potential therapeutic role in ALI.<sup>214</sup> Statins also appear to diminish the stabilization of lipid raft formation and prevent the prenylation of signaling molecules with subsequent downregulation of gene expression and immune activation and regulation, which result in

reduced expression of adhesion molecules, chemokines, and cytokines, and effects on cell proliferation or apoptosis.<sup>215</sup> Statins can also significantly reduce ROS/NOS generation, cytokine expression such as TNF- $\alpha$  and IL-6, and upregulation of inflammatory mediators such as cyclooxygenase-2 in the pulmonary inflammation model.<sup>216</sup>

The anti-inflammatory effect of atorvastatin is antagonized by PPAR- $\gamma$  antagonists which indicates its anti-inflammatory effects are mediated via PPAR- $\gamma$  receptors. The therapeutic target of atorvastatin may be HO-1. A previous study using the zymosan-injected air pouch to trigger inflammation found that pretreatment with atorvastatin attenuated cell influx and the expression of proinflammatory cytokines and chemokines along with induction of HO-1 in the cells of the exudate of the air pouch, effects which were reversed by exposure to tin protoporphyrin IX (SnPPiX), an heme oxygenase inhibitor.<sup>217</sup> Our recent study also revealed that HO-1 induction by mevastatin through the Nrf2/ARE axis was regulated by the p47<sup>phox</sup>/Nox2/ROS-dependent activation of c-Src/PDGFR/PI3K/Akt<sup>112</sup> or by c-Jun activation activated by the PKC/Pyk2/p38 MAPK- or JNK1/2-dependent pathways and led to AP-1-binding on the HO-1 promoter region<sup>113</sup> using HPAEpiCs and animal studies. Further, mevastatin can suppress inflammatory responses mediated by TNF $\alpha$ .<sup>112,113</sup> Chemotaxis is also attenuated by statins, as demonstrated by the rosuvastatin-induced decrease in the number of macrophages, lymphocytes, neutrophils, eosinophils, and total inflammatory cells recruited into BALF, as well as the lower levels of TNF- $\alpha$ , IL-4, IL-5, and IL-13 in BALF.<sup>218</sup> Treatment with another statin, simvastatin, also prevented the recruitment of leukocytes to the lung, abrogated pulmonary endothelial injury, attenuated pulmonary hyperpermeability,<sup>219,220</sup> reduced pulmonary cytokine levels such as IL-13 and TGF- $\beta$ 1 in patients with lung fibrosis,<sup>221,222</sup> and improved oxygenation in mechanically ventilated mice.<sup>223</sup> The effectiveness of simvastatin on pulmonary disorders could also be primarily mediated through an HO-1 related pathway. A study using pulmonary hypertension models induced by chronic hypoxia and monocrotaline administration in rats indicated that exposure to simvastatin significantly improved right ventricular hypertrophy and pulmonary arterial hypertension, effects that were associated with significant induction of HO-1 protein levels and activity, which were abolished by SnPP.<sup>224</sup> Another study also



demonstrated that simvastatin could inhibit pulmonary artery smooth muscle cells (PASMCs) proliferation induced by serotonin stimulation in a dose-dependent manner, which was accompanied by the parallel induction of HO-1/p21<sup>WAF1</sup>, an effect that was reversed by treatment with Tin-protoporphyrin (SnPP, a selective inhibitor of HO-1).<sup>225</sup> These statins mentioned above including atorvastatin, mevastatin, simvastatin, and rosuvastatin can enhance HO-1 activity in different extra-vascular tissues including the lungs.<sup>226</sup> Thus, HO-1 induction represents a crucial mechanism by which statins can exert anti-oxidative and anti-inflammatory effects on the management of inflammatory diseases including pulmonary disorders, such as ALI/acute respiratory distress syndrome<sup>60,227,228</sup> The HO system mitigates the effects induced by oxidative stress and its detrimental effects in pulmonary disorders, which could be mediated by decreasing the levels of heme and increasing levels of bilirubin and CO to achieve anti-inflammatory, anti-oxidant, and anti-apoptotic effects.<sup>227</sup>

Fessler et al determined that lovastatin inhibited aerosolized LPS-induced lung inflammation and caused impairment of host defenses via the inhibition of the mevalonate pathway, which was associated with the reduction of parenchymal MPO and microvascular permeability, and changes in cytokine levels triggered by LPS. Moreover, lovastatin also could inhibit chemotaxis, bactericidal killing capacity, actin polymerization, and Rac activation.<sup>229</sup> Therefore, these properties of statins might reduce the possibility of cancerogenesis in lung tissue and may attenuate the progression of COPD. Indeed, in past decades, several clinical studies evaluating oral statins as a potential treatment for chronic pulmonary disorders such as PH, ALI, COPD, and asthma have been conducted, but the findings and conclusions derived from these trials were inconsistent. For example, Xu et al found that among COPD patients treated with statins, those who were current or former smokers exhibited interstitial lung abnormalities (ILA), and pretreatment with statin enhanced lung inflammation and fibrosis induced by bleomycin in vivo and NLRP3-inflammasome activation and augmented mtROS generation.<sup>230</sup> Moreover, a review of randomized controlled trials extracted from the Cochrane library (2019) concluded that statin use resulted in a decrease in IL-6 and CRP levels, but that the findings did not translate into a clinical application for COPD patients because of the lack of a significant statistical difference in

mortality, FEV1, functional capacity, the number of exacerbations, or quality of life. The authors concluded that additional randomized controlled trials are necessary to explore this issue.<sup>231</sup> Sub-therapeutic levels and low systemic bioavailability of statins in the airways following oral delivery of statins may have contributed to these conflicting findings. Therefore, an inhalation formulation of statins may overcome these problems in bioavailability. In several animal experiments, the inhalation of statins such as simvastatin pravastatin, rosuvastatin, pitavastatin, and atorvastatin induced better effects on anti-pulmonary inflammation.<sup>232</sup> Thus, statins could be efficacious in the treatment of lung inflammatory disorders and the development of inhalation formulations is warranted.

## Chinese Herbal Medicines

### Salvianolic Acid A/B

Both salvianolic acid B (SalB) and SalA,<sup>16</sup> major bioactive compounds isolated from *Salviae Miltiorrhizae* (also called Danshen) belonging to the Chinese herb Radix, have been reported to exhibit anti-oxidative and anti-inflammatory effects.<sup>233</sup> Endothelial-to-mesenchymal transition (EndMT) participates in the remodeling of the pulmonary vessel, an effect that is partially attributed to inflammatory and oxidative stress in endothelial cells. SalA,<sup>16</sup> a polyphenol compound, stimulates the translocation of Nrf2 and subsequent up-regulation of HO-1 to inhibit EndMT-mediated pulmonary vascular remodeling.<sup>87</sup> SalA also prevents pulmonary fibrosis by arresting the cell cycle and promoting apoptosis in fibroblasts via the decreased expression of the anti-apoptotic Bcl-2, cyclin B1, cyclin D1, and cyclin E1 protein, and cleaved caspase-3 protein and increased expression of p53 and p21.<sup>234</sup> Furthermore, sortase A activity can be inhibited by SalA (IC<sub>50</sub> = 5.75 µg/mL) and bacterial adhesion to fibrinogen is repressed by SalA, which prevents the ability of *Staphylococcus aureus* to infect A549 cells.<sup>235</sup> Zhao et al revealed that besides SalA, pretreatment with SalB in ALI model rats, attenuated oxidative stress by enhancing the levels of GSH peroxidase, CAT, and SOD, and also blocked lung fibrosis by reducing the protein expression of  $\alpha$ -smooth muscle actin, endogenous TGF- $\beta$ 1 production, and type I collagen.<sup>236</sup> Further, SalB exerted anti-inflammatory roles on pulmonary fibrosis in a bleomycin-treated

mouse model by protecting endothelial cells from oxidative stress injury, mediated by inhibiting the expression of pro-inflammatory cytokines and endothelial permeability via MAPK and NF- $\kappa$ B signaling pathways.<sup>40</sup> Zhang et al also revealed that SalB inhibited cigarette smoke (CS)-induced inflammatory cells infiltration, MCP-1, IL-6, IL-1 $\beta$ , and TNF- $\alpha$  synthesis, and up-regulation of total GSH production induced by CS, via up-regulation of the Nrf-2/HO-1 axis and also by suppressing the NF- $\kappa$ B activation induced by CS.<sup>237</sup> Besides regulating Nrf2/Nox4 redox balance, SalB inhibited the TGF- $\beta$ 1/Smad3 signaling pathway, which led to protection against pulmonary injury induced by paraquat.<sup>238</sup>

## Asiatic Acid (AA)

Asiatic acid (AA) is a triterpenoid compound isolated from *Centella Asiatica*.<sup>239</sup> AA has been reported to exert diverse pharmacological activities, such as anti-oxidative, anti-cancer, hepatoprotective, and anti-inflammatory effects.<sup>240</sup> AA has been also been shown to attenuate fibrosis progression.<sup>241</sup> In a bleomycin model of pulmonary fibrosis, AA ameliorated pulmonary fibrosis by inhibiting inflammatory and pro-fibrotic signaling pathways, including the expression of TGF- $\beta$ 1 and that of matrix metalloproteinase (MMP)-1,  $\alpha$ -SMA, type III collagen, and type II collagen, and the formation of the NLRP3 inflammasome, as well as the inactivation of ERK1/2 and Smads.<sup>242</sup> AA also reduced ROS generation and neutrophil elastase activity and attenuated MCP-1 expression, as well as the recruitment of inflammatory cells through decreased MAPKs and NF- $\kappa$ B activation and increased expression of SOD3 and HO-1 in lung tissue.<sup>41</sup> Xia et al revealed that AA significantly reduced  $\alpha$ -smooth muscle actin and type I collagen expression by inhibiting ROS generation and the TGF- $\beta$ 1/Smad2/3 signaling pathway.<sup>243</sup> Jiang et al determined that AA might reduce the levels of MPO, inflammatory cytokines, ROS, and MDA, and may inhibit neutrophil infiltration, while it promotes an increase in SOD and CAT levels<sup>109</sup> by upregulating Nrf2 levels and downregulating NLRP3 inflammasome protein expression in ALI in rats.<sup>244</sup>

## Celastrol

Celastrol, a pentacyclic triterpenoid, was extracted from the roots of *Tripterygium wilfordii*, which is a component of traditional Chinese medicine and can significantly

ameliorate NF- $\kappa$ B<sup>245</sup> and NLRP3 activities<sup>246</sup> to induce significant anti-inflammatory activity.<sup>247</sup> Exposure to celastrol reduced levels of the cytokines MCP-1, TNF- $\alpha$ , and IL-8 in the BALF and serum and upregulated levels of SOD and CAT, which were accompanied by the attenuation of the Ednrb/Kng1 signaling pathway in COPD mouse models.<sup>248</sup> In another bleomycin-induced pulmonary fibrosis animal model, celastrol demonstrated antioxidant and anti-fibrotic effects against pulmonary fibrosis. Furthermore, celastrol decreased the expression of the inflammatory mediators MMP-2/9 and TNF- $\alpha$  and it also induced Nrf2 expression, which rescues the activities of Phase II enzymes including NAD(P)H:quinone oxidoreductase 1 (NQO1), HO-1, and GSTs.<sup>88</sup> Celastrol also reduced the protein levels of Bax and caspase-3 activity to induce anti-inflammatory and anti-apoptotic effects in burn-induced lung injury.<sup>249</sup>

## Fisetin

Fisetin (3,7,3',4'-tetrahydroxy flavone) is a flavonoid commonly found in various types of vegetables and fruits such as strawberries, cucumbers, onions, grapes, persimmons, and apples and plants such as smoke trees. Various studies in vivo and in vitro have demonstrated that fisetin possesses diverse pharmacological activities including anti-inflammatory,<sup>250</sup> anticancer,<sup>251</sup> and antioxidative effects.<sup>252</sup> Pretreatment with fisetin in COPD patients markedly inhibited increases in serum concentrations of TNF- $\alpha$  induced by LPS via inhibition of the nuclear enzyme PARP-1.<sup>253</sup> Fisetin also reduced neutrophil levels and infiltration of macrophages and also attenuated MPO activity in the LPS-induced ALI model by inhibiting the activation of NF- $\kappa$ B signaling and the TLR4 expression in pulmonary tissues.<sup>254</sup> Huang et al also determined that fisetin treatment decreased the infiltration of neutrophils, monocytes, and eosinophils by inhibiting the MyD88/NF- $\kappa$ B signaling pathway to alleviate airway inflammation.<sup>255</sup> Conversely, Hussain et al revealed that in lungs exposed to CS, fisetin attenuated inflammation and oxidative stress to protect the lung from CS-mediated injury via the Nrf2-dependent expression of antioxidative genes (HO-1, glutathione peroxidase-2, reduced GSH, SOD) to reduce the infiltration of inflammatory cells and cytokine expression.<sup>89</sup>

## Galangin

Galangin (3,5,7-trihydroxyflavone) is found in *Alpinia officinarum* and honey in high concentrations and is

a member of the flavonol class of flavonoids, and has been used as a spice and herbal medicine for various diseases.<sup>256</sup> Growing evidence shows that galangin exhibits anti-fibrotic, anti-oxidant, and anti-inflammatory activities, which are beneficial for various disorders.<sup>44</sup> Galangin has been shown to attenuate oxidative damage and inflammation via upregulation of Nrf2/HO-1 in various tissues including the lungs.<sup>90,91</sup> Galangin acts as an anti-remodeling agent in an asthma model, as it has been shown to inhibit the TGF- $\beta$ 1-ROS-MAPK pathway and attenuate  $\alpha$ -SMA expression, collagen deposition, and goblet cell hyperplasia, in addition to the suppression of MMP-9 and vascular endothelial growth factor (VEGF) expression.<sup>257</sup> A report indicated that in an OVA-induced allergic asthma model, oral administration of galangin notably attenuated goblet cell hyperplasia, inflammation, and airway hyperresponsiveness via the suppression of TNF- $\alpha$ , IL-4, IL-5, IL-13, IL-17, NO, ROS, immunoglobulin E,<sup>123</sup> and eosinophil peroxidase, and an increase in interferon (IFN)- $\gamma$  in a PPAR- $\gamma$ -dependent manner.<sup>258</sup>

## Kaempferol

Kaempferol (KPF), a flavonol, is present in significant amounts in beans, apples, tea, strawberries, and broccoli<sup>259</sup> and is known to be beneficial in diseases such as inflammation, allergies, and cancer. Growing evidence has indicated that KPF exerts anti-inflammatory effects on various experimental disease models in vivo and in vitro.<sup>260,261</sup> Several lines of evidence have shown that KPF has protective effects against apoptosis and allergic reactions via HO-1 induction in various types of cells.<sup>92–95</sup> Qian et al determined that in ALI induced by LPS, KPF disrupts activation of TGF- $\beta$ -activated kinase 1 (TAK1) and TNF receptor-associated factor 6 (TRAF6)-mediated polyubiquitination, and the activation of subsequent downstream NF- $\kappa$ B and MAPK signaling to reduce cytokine production and inflammatory injury.<sup>45</sup> Zhang et al also found that KPF could significantly attenuate enhancement of NF- $\kappa$ B p65 DNA binding activity by inhibiting the upregulation of TLR4/MyD88/phosphorylation of I $\kappa$ B $\alpha$ /NF- $\kappa$ B p65, and the MAPKs phosphorylation, leading to attenuation of ROS production and cytokine overexpression in an H9N2 swine influenza virus-induced ALI model.<sup>262</sup> Expression of inflammatory mediators such as COX-2,<sup>133</sup> was alleviated by KPF treatment in allergic pulmonary disorders.<sup>263</sup> In another LPS-induced ALI

mice model, KPF mitigated the activation of the MAPKs and NF- $\kappa$ B signaling pathways to alleviate oxidative stress, cytokine production, and leukocyte infiltration in lung tissues.<sup>264</sup> The flavonoid kaempferol-3-O-glucorhamnoside, derived from the plant *Thesium chinense* Turcz, is a KPF derivative and also suppresses NF- $\kappa$ B and MAPK phosphorylation to attenuate the production of inflammatory cytokines and overall oxidative stress in the pneumonia model infected by *Klebsiella pneumoniae* both in vitro and in vivo.<sup>265</sup>

## Luteolin

Luteolin is a natural flavonoid compound (also known as 3',4',5,7-tetrahydroxyflavone) and widely distributed in the leaves of many types of plants, for example, celery, thyme, dandelion, and basil.<sup>266</sup> Growing evidence has demonstrated that the pharmacological activities of luteolin include anti-oxidative, anti-inflammatory, anti-tumor effects, and anti-ischemic effects in response to vascular injury.<sup>267</sup> Luteolin pretreatment can promote the expression of HO-1 to prevent apoptosis,<sup>96</sup> and exerts anti-inflammatory and antioxidant effects<sup>268</sup> in in vivo and in vitro. Hence, luteolin has been applied to the treatment of various diseases, such as cancer, hypertension, and inflammatory diseases.<sup>266</sup> Liu and Meng found that luteolin mitigates the activation of the NF- $\kappa$ B signaling pathway induced by LPS by down-regulating miR-132 in a bronchopneumonia murine model.<sup>269</sup> Luteolin, in primary cultured mouse lung fibroblasts, also inhibited expression of vimentin, type I collagen, and  $\alpha$ -SMA induced by TGF- $\beta$ 1 in vitro and in a bleomycin-treated C57BL/6J mice model, and also effectively attenuated neutrophil infiltration and expression of IL-6 and TNFR in vivo, leading to alleviation of experimental lung fibrosis.<sup>270</sup> In the mercuric chloride-induced lung injury mouse model, luteolin treatment was responsible for the reduction of MPO, inflammatory cytokines, and MDA levels and for the increase of SOD and GSH by preventing NF- $\kappa$ B activation, while also activating the Akt/Nrf2 pathway.<sup>271</sup> *Glossogyne tenuifolia* ethanol extract which contains luteolin as its major component has been demonstrated to possess potent anti-inflammatory and antioxidative activities by blocking the NF- $\kappa$ B signaling pathway.<sup>272</sup>

## Madecassoside

Madecassoside is derived from *Centella Asiatica* (Umbelliferae) and is a triterpene compound. It possesses

pleiotropic bioactivities and is effective in many experimental disease models.<sup>273–275</sup> Madecassoside has been shown to exert anti-inflammatory activities by activating Nrf2/HO-1 signaling in different disease models.<sup>97,98</sup> Further, madecassoside can ameliorate bleomycin-induced pulmonary fibrosis by attenuating oxidative stress, inflammation, and subsequent overexpression of TGF- $\beta$ 1.<sup>276</sup> Treatment with madecassoside can also reduce the expression of TGF- $\beta$ 1 and  $\alpha$ -SMA, p-Smad2 and p-Smad3 levels, MPO activity, and MDA levels, as well as increase GSH levels and SOD activity in lung tissues.<sup>276</sup>

## Oleanolic Acid

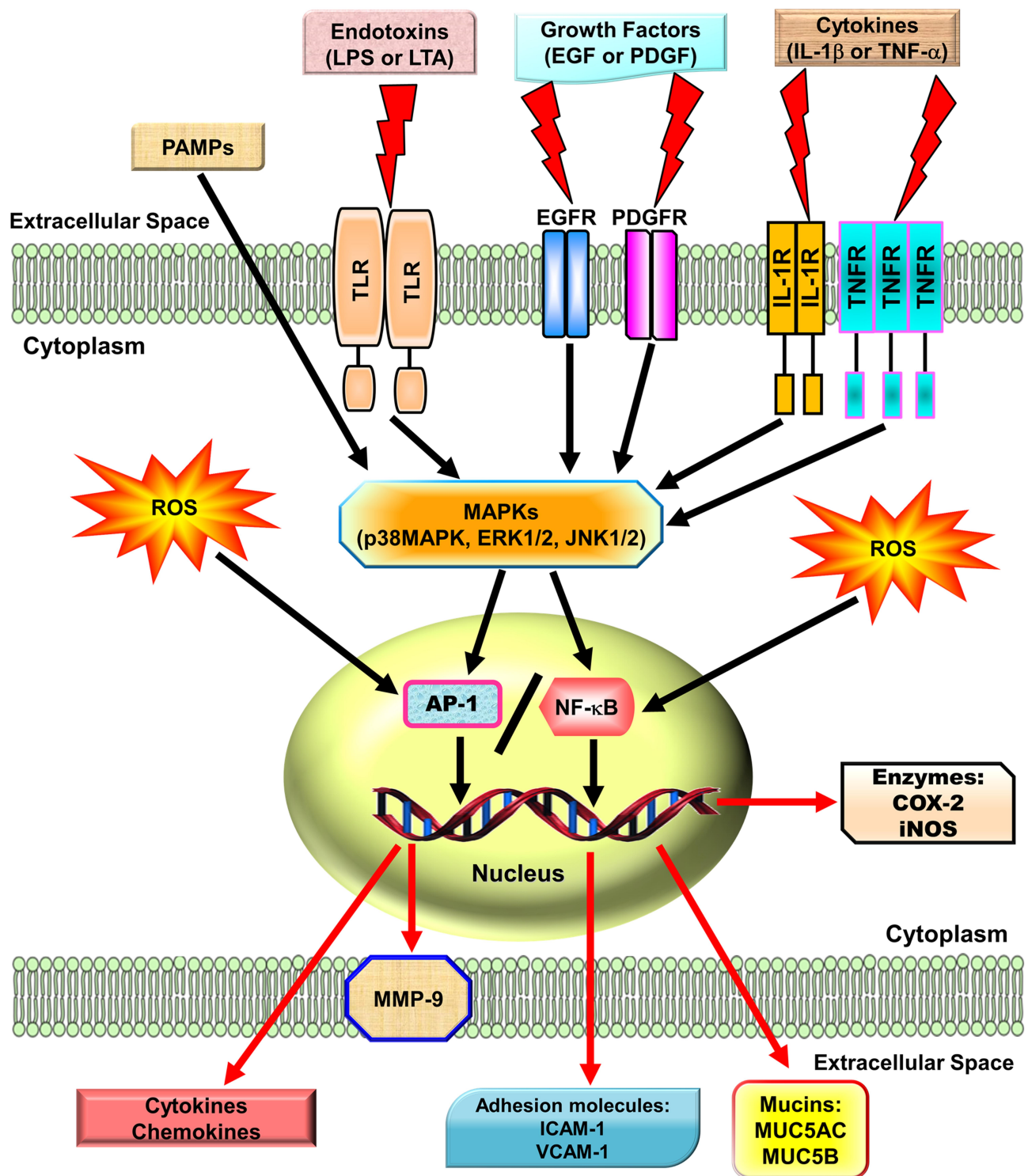
Oleanolic acid (OA) was isolated from different medicinal plants and is a biologically active natural pentacyclic triterpenoid compound.<sup>277</sup> Growing evidence has shown that OA has pleiotropic effects including anticancer, anti-inflammation, anti-diabetes, and antiasthmatic effects and also exerts hepatoprotective effects.<sup>278</sup> GATA-binding protein 3 (GATA-3), a mediator of allergic airway inflammation, is a crucial factor in vivo.<sup>279</sup> OA has been demonstrated to exert anti-inflammatory and anti-asthmatic activity via inhibition of GATA-3 and retinoic acid receptor-related orphan receptor gamma-t pathways in an OVA-induced airway inflammation model.<sup>280</sup> Furthermore, OA has been shown to protect cells from acetaminophen-induced hepatotoxicity via induction of Nrf2-dependent HO-1.<sup>99</sup> Studies have also demonstrated that OA induces HO-1 expression and protects from ROS-induced cell death in rat vascular smooth muscle cells.<sup>100</sup> Santos et al revealed that OA administration has anti-oxidative effects by attenuating ROS generation and restoring the reduced GSH/oxidized glutathione ratio and CAT activity in experimental ALI induced by paraquat.<sup>281</sup> Furthermore, OA also diminished TNF- $\alpha$ , macrophage migration inhibitory factor, IL-6, INF- $\gamma$ , and TGF- $\beta$  mRNA expression in lung tissues.<sup>281</sup> OA can also modulate oxidative stress by reducing inducible NOS expression and enhancing SOD.<sup>282</sup> OA exerts significant antioxidant and anti-inflammatory activities by blocking the NF- $\kappa$ B signaling pathway.<sup>272</sup> In addition, in a murine model of pulmonary fibrosis and inflammation induced by polyhexamethylene guanidine phosphate, OA acetate effectively reduced elevation of cytokines and the activation of the NLRP3 inflammasome.<sup>283</sup> The Chinese medicinal preparation *Eriobotrya japonica* which contains OA as one of its six main constituents

acts on the actin cytoskeleton, tight junctions, focal adhesion, MAPK pathway, and TGF- $\beta$  pathway to exert anti-inflammatory effects and cough suppression.<sup>48</sup> Lee et al demonstrated that *Eriobotrya japonica* suppresses  $\kappa$ B- $\alpha$  phosphorylation and NF- $\kappa$ B activity to inhibit cytokine production.<sup>284</sup> In the N-methyl-D-aspartate (NMDA)-induced ALI mice model, OA attenuated NMDA-induced oxidative stress, cytokine expression, and inflammatory cell infiltration by activating SIRT1 and reducing NF- $\kappa$ B acetylation.<sup>285</sup>

## Oleanolic Acid Derivatives

As indicated above OA has been used to treat liver disorders due to its modest biological activities in humans. Bardoxolone methyl [CDDO-Me; 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid methyl ester] is a derivative of OA; it has broad pharmacological functions including antiproliferative, anti-tumorigenic, antioxidant, anti-tumor, and anti-inflammatory effects.<sup>286</sup> CDDO-Me has been shown to induce Nrf2/HO-1 upregulation in in vitro and in vivo.<sup>287</sup> CDDO-Me effectively inhibits the ALI induced by LPS in vivo, its underlying anti-inflammatory activity might result from the reduction of NO, IL-6, IL-1 $\beta$ , and TNF- $\alpha$  levels via the attenuation of MAPK, Akt, and NF- $\kappa$ B pathways.<sup>288</sup> 2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) is another synthetic triterpenoid. A previous study revealed that CDDO, at nanomolar concentrations, increased the expression of HO-1 both in vitro and in vivo.<sup>102</sup> Nichols et al found that in in vitro cystic fibrosis cell culture models, the synthetic triterpenoid CDDO limited inflammation by reducing NF- $\kappa$ B activation while increasing Nrf2 activity.<sup>289</sup> In another model of lung fibrosis induced by bleomycin, triterpenoid CDDO-Me treatment inhibited levels of cytokines IL-6 and keratinocyte-derived chemokine, the pro-fibrotic cytokine TGF $\beta$ , and mRNA expression of fibronectin and  $\alpha$ -smooth muscle actin, which led to the attenuation of histological fibrosis and improvement of lung function.<sup>290</sup> In addition, Wang et al using a radiation-induced pulmonary inflammation and fibrosis animal model also showed that CDDO-Me exerted anti-inflammatory and anti-fibrotic effects by suppressing the expression and secretion of proinflammatory cytokines IL-6 and TGF- $\beta$ , and elevating the production of cytokines such as IL-10, which has anti-inflammatory properties, and downregulating the expression of





**Figure 1** The roles of ROS, pro-inflammatory mediators, and transcription factors AP-1 and NF- $\kappa$ B in pulmonary inflammatory diseases. Pathogen-activated molecular patterns (PAMPs), including endotoxins (LPS or LTA), growth factors (EGF or PDGF), and cytokines (IL-1 $\beta$  or TNF- $\alpha$ ), activate downstream pathways (p38 MAPK, JNK 1/2, and ERK 1/2) via their respective receptors (TLR, EGFR, PDGFR, IL-1R, and TNFR) to promote transcription factors NF- $\kappa$ B and AP-1 activities also activated by ROS, leading to genes transcription (including cytokines, chemokines, MMP-9, COX-2, iNOS, ICAM-1, VCAM-1, MUC5AC, and MUC5B) and pulmonary inflammation.

**Abbreviations:** LPS, lipopolysaccharides; LTA, lipoteichoic acid; EGF, epidermal growth factor; TNF- $\alpha$ , tumor necrosis factor  $\alpha$ ; IL-1 $\beta$ , interleukin 1 $\beta$ ; PDGF, platelet-derived growth factor; TLR, Toll-like receptor; AP-1, activator protein 1; MMP-9, matrix metalloproteinases-9; NF- $\kappa$ B, nuclear factor- $\kappa$ B; ROS, reactive oxygen species; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule -1; MUC5AC, mucin 5AC; MUC5B, mucin 5B.

profibrotic genes, including collagen I,  $\alpha$ -SMA, and fibronectin mRNA levels.<sup>291</sup>

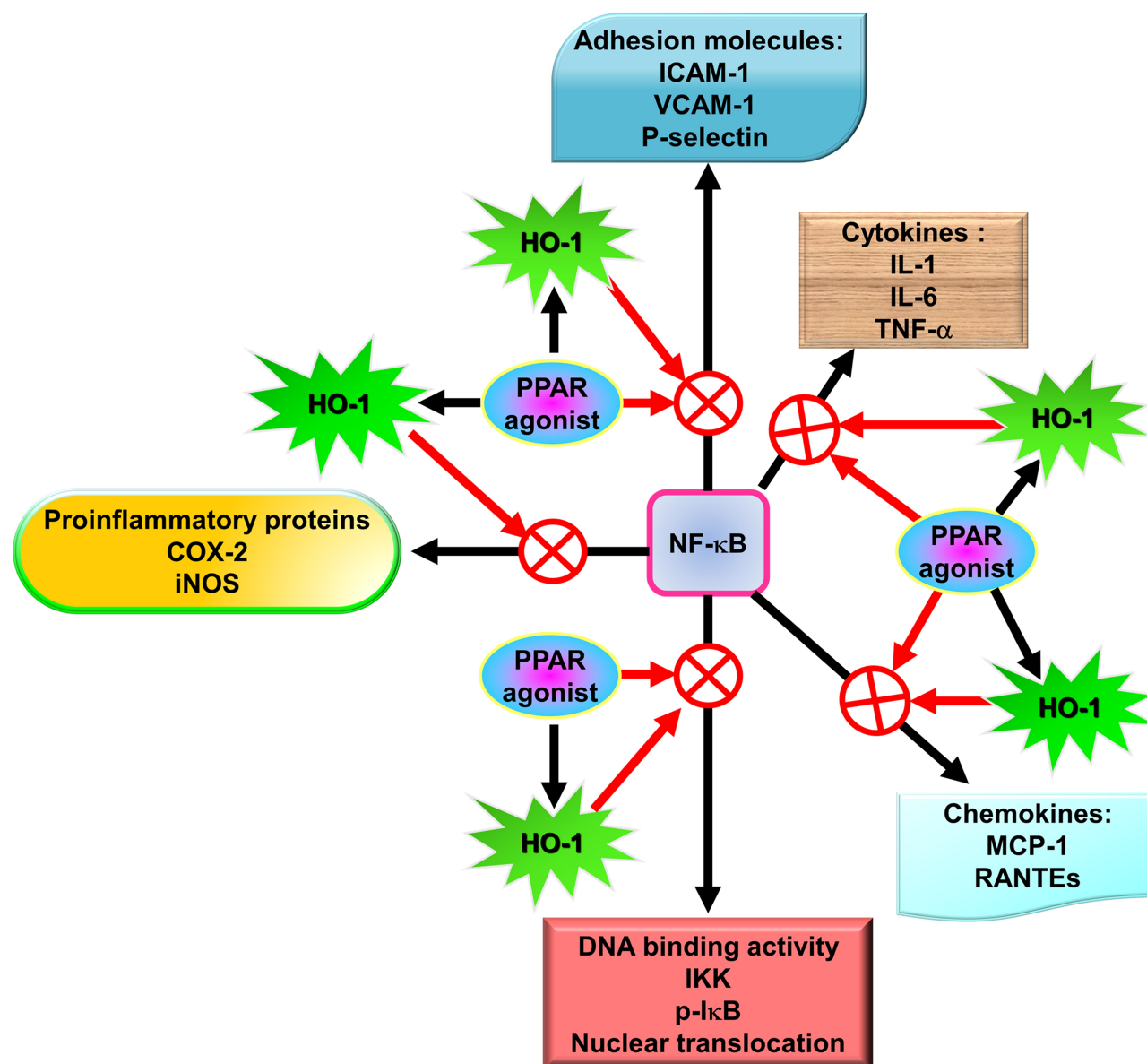
## Saikosaponin A

Saikosaponin A (SSa), isolated from *Radix Bupleuri* (RB), is a triterpenoid saponin and exhibits several pharmacological activities, such as antioxidative and anti-inflammatory effects.<sup>292</sup> SSa significantly attenuated the infiltration of inflammatory cells, IL-1 $\beta$ , TNF- $\alpha$ , and NO production induced by CS and it also inhibited the MDA

and MPO activity induced by CS in lung tissues via upregulating the expression of HO-1 and Nrf2 and inhibiting NF- $\kappa$ B activity.<sup>101</sup>

## Pristimerin (Pris)

Pristimerin (Pris) was isolated from plants that belong to the Hippocrateaceae or Celastraceae families and is a natural quinone-methide triterpenoid derivative.<sup>293</sup> Pris possesses numerous biological activities including antioxidant, antibacterial, and anti-cancer effects.<sup>294–296</sup>



**Figure 2** The functions of PPARs agonists in pulmonary inflammation. PPARs agonists and PPARs agonist-induced HO-1 upregulation can inhibit NF- $\kappa$ B activity via blocking IKK activity and I $\kappa$ B phosphorylation, leading to suppression of NF- $\kappa$ B nuclear translocation and DNA binding activity and in turn reduction of gene expression including MCP-1, iNOS, VCAM-1, ICAM-1, P-selectin, IL-1, IL-6, TNF- $\alpha$ , COX-2, and RANTES.

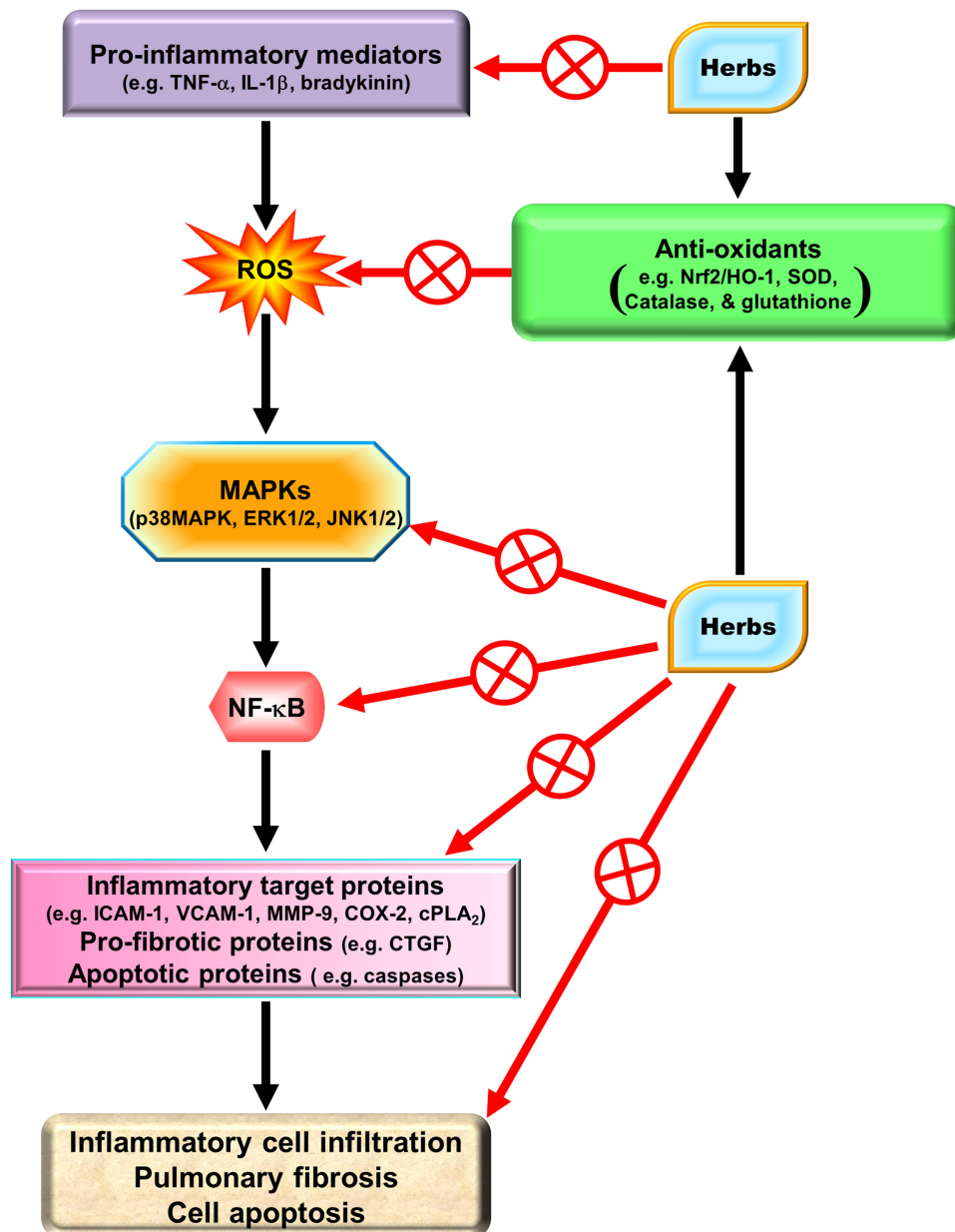
**Abbreviations:** TNF- $\alpha$ , tumor necrosis factor  $\alpha$ ; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; IL, interleukin; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; HO, heme oxygenase; NF- $\kappa$ B, nuclear factor- $\kappa$ B; RANTES, regulated upon activation normal T-cell expressed and secreted; MCP-1, monocyte chemoattractant protein-1; IKK, I $\kappa$ B kinase.

Pris exerts its anti-oxidative, anti-inflammatory, and anti-apoptotic effects via induction of HO-1 in various tissue injury models.<sup>49,103</sup> Our recent study also suggested that Pris possesses anti-neuroinflammatory and anti-oxidative effects<sup>297</sup> through HO-1 up-regulation in rat brain astrocytes (unpublished data). Further, Pris protected against the LPS-induced ALI in mouse models via anti-oxidant, anti-inflammatory, and anti-apoptotic effects. Furthermore, Pris treatment attenuated the

production of pro-inflammatory cytokines including IL-6 and TNF- $\alpha$ , and elevation of pro-apoptotic proteins including Bax and caspase-3. Pris has also been shown to up-regulate Bcl2 inhibited by LPS.<sup>298</sup>

## Conclusions

A growing number of studies have indicated that both exogenous and endogenous ROS participate in the pathogenesis of pulmonary disorders, such as ARDS, COPD,



**Figure 3** The anti-inflammatory, anti-fibrotic, and anti-apoptotic mechanisms of Chinese herbs in the lungs. Herbs can target individual signal molecules including ROS, MAPKs, and NF- $\kappa$ B as well as pro-inflammatory mediators to block the expression of pro-inflammatory proteins, pro-fibrotic proteins, and pro-apoptotic proteins.

**Abbreviations:** COX-2, cyclooxygenase-2; cPLA<sub>2</sub>, cytosolic phospholipase A<sub>2</sub>; CTGF, connective tissue growth factor; HO, heme oxygenase; ICAM-1, intercellular adhesion molecule-1; IL-1, interleukin-1; JNKs, c-Jun NH2-terminal kinases; MAPKs, mitogen-activated protein kinases; MMP, matrix metalloproteinase; NF- $\kappa$ B, nuclear factor- $\kappa$ B; Nrf2, NF-E2-related factor 2; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; VCAM-1, vascular cell adhesion molecule-1.

**Table I** The Effects of Herbal Compounds in Pulmonary Inflammation

Compound	Action	references
Salvianolic acid A/B	↑Nrf2 translocation, ↑HO-1, ↓pulmonary vascular remodeling via inhibiting EndMT	[87,237,238]
	↓pulmonary fibrosis, ↓cyclin D1, ↓cyclin E1, ↓cyclin B1, ↓Bcl-2 protein, ↑p53, ↑p21, ↑cleaved caspase-3 protein	[234]
	repress the adhesion of bacteria	[235]
	↑SOD, ↑catalase, ↑glutathione peroxidase ↓ type I collagen I, ↓endogenous TGF-β1, ↓α-SMA	[236,238]
	↓MAPK and NF-κB signaling pathways	[40,237]
	↓TNF-α, ↓IL-6, ↓IL-1β, ↓MCP-1	[237]
Asiatic acid	↓pulmonary fibrosis	[241,242]
	↓TGF-β1, ↓Collagen I, ↓Collagen III, ↓α-SMA, ↓TIMP-1, ↓NLRP3 inflammasome, ↓Smads and ERK1/2	[242–244]
	↓ROS, ↓neutrophil elastase (NE) activity, ↓MCP-1, ↓recruitment of inflammatory cells, ↓MAPKs, ↓NF-κB, ↑Nrf2, ↑HO-1, ↑SOD3, ↑catalase	[41,243,244]
Celastrol	↓NF-κB signaling pathway, ↓NLRP3 activity	[245–246]
	↓IL-8, ↓TNFα, ↓MCP-1, ↑SOD, ↑catalase, ↓EdnrB/Kng1 signaling pathway	[248]
	↓MMP 2/9, ↑Nrf2, ↑HO-1, ↑GSTs, ↑NQO1	[88]
	↓Bax, ↓caspase-3	[249]
Fisetin	↓TNFα, ↓PARP-1	[253]
	↓neutrophils and macrophage infiltration, ↓MPO activity, ↓TLR4 expression, ↓NF-κB	[254,255]
	↑Nrf2, ↑HO-1, ↑glutathione peroxidase-2, ↑reduced glutathione, ↑SOD	[89]
Galangin	↓TGF-β1-ROS-MAPK pathway, ↓goblet cell hyperplasia, ↓collagen deposition, ↓α-SMA expression, ↓VEGF, ↓MMP-9	[257]
	↓IL-4, 5, 13, 17, ↓TNF-α, ↓NO, ↓ROS, ↓EPO, ↓IgE, ↑IFN-γ, ↑PPARγ activity	[258]
Kaempferol	↓TAK1, ↓NF-κB, ↓MAPK, ↓cytokine production	[45,262,264,265]
	↓ROS	[262]
	↓Cyclooxygenase-2	[133]
Luteolin	↓NF-κB signaling pathway, ↓miR-132	[269]
	↓TGF-β1, ↓α-SMA, ↓type I collagen, ↓vimentin, ↓neutrophil infiltration, ↓TNF-R, ↓IL-6, ↓lung fibrosis	[270]
	↓MPO, ↓inflammatory cytokines, ↓MDA, ↑SOD, ↑glutathione, ↓NF-κB activation, ↑AKT/Nrf2 pathway	[271,272]
Madecassoside	↓pulmonary fibrosis, ↓oxidative stress ↓α-SMA, ↓TGF-β1, ↓phosphorylations of Smad2 and Smad3, ↓MPO, ↓MDA, ↑SOD, ↑glutathione level	[276]
Oleanolic acid	↓GATA-3 and RORγt pathways	[280]
	↓ROS, ↑reduced glutathione/oxidized glutathione ratio, ↑catalase, ↓TNF-α, ↓macrophage migration inhibitory factor, ↓IL-6, ↓interferon-γ, ↓TGF-β	[48,281]
	↓iNOS, ↑SOD	[282]
	↓NF-κB	[272,284,285]
	↓cytokines, ↓NLRP3 inflammasome	[283]
	↑SIRT1	[285]

(Continued)



**Table 1** (Continued).

Compound	Action	references
Saikosaponin A	↓cell infiltration, ↓NO, ↓TNF- $\alpha$ , ↓IL-1 $\beta$ , ↓MPO, ↓MDA, ↓NF- $\kappa$ B, ↑Nrf2 and HO-1	[101]
CDDO-Me	↓NO, ↓TNF- $\alpha$ , ↓IL-1 $\beta$ , ↓IL-6, ↓NF- $\kappa$ B, ↓Akt, ↓MAPK pathways	[288–291]
	↑Nrf2 activity	[289]
	↓TGF $\beta$ , and ↓ $\alpha$ -SMA, ↓fibronectin, ↓fibrosis	[290,291]
Pristimerin	↓TNF- $\alpha$ , ↓IL-6, ↓Bax, ↓caspase-3, ↑Bcl2	[298]

**Abbreviations:** NE, neutrophil elastase; TGF- $\beta$ 1, transforming growth factor- $\beta$ 1;  $\alpha$ SMA,  $\alpha$ -smooth muscle actin; SOD, superoxide dismutase; MDA, Malondialdehyde; MPO, myeloperoxidase; ROR $\gamma$ t, retinoic acid receptor-related orphan receptor gamma-t; iNOS, inducible nitric oxide synthase; “↓”, decrease; “↑”, increase.

and asthma.<sup>60</sup> AP-1 and NF- $\kappa$ B are well known as vital regulators of inflammatory mediators, including enzymes (COX2, MMP-9, and NOS), chemokines, cytokines, mucins, and receptors, which all participate in the pathological mechanisms of these respiratory diseases (Figure 1). NF- $\kappa$ B is activated by several factors, such as ROS and pathogen-associated molecular pattern (PAMP), through downstream signaling pathways (Figure 1). The remodeling of damaged tissue, as occurs in pulmonary fibrosis, also plays an important role in lung injury insults including COPD, asthma, and ARDS. TGF- $\beta$ , CTGF, and endothelin-1 are important players in these processes. These diseases all have a poor prognosis and a high mortality rate. Therefore, it is crucial to develop specific inhibitors as an effective strategy for the treatment of inflammatory disorders. Currently, the literature has indicated that antioxidants are an effective defense against these diseases. These antioxidants include enzymatic antioxidants, such as CAT, SOD, glutathione peroxidase, and HO-1, and non-enzymatic antioxidants, including vitamins A, C, and E, and GSH. A growing number of studies have indicated that HO-1 is an effective antioxidant, and based on these findings, several medicines and Chinese herbs can also induce the upregulation of its expression. Herein, we reviewed several potential HO-1 inducers, including PPAR agonists (Figure 2), statins, and Chinese herbal medicines (Figure 3 and Table 1). Although these studies support their effects on lung injury in animal models, there is currently no evidence in human respiratory diseases. Further clinical studies are necessary to identify the pharmacological activities of these medicines and herbal compounds in these pulmonary inflammatory diseases.

## Abbreviations

AA, asiatic acid; AFC, alveolar fluid clearance; ALI, acute lung injury; AOR, adjusted odds ratio; AP-1, activator protein 1; APCs, antigen-presenting cells; ARDS, acute respiratory distress syndrome; AREs, antioxidant response elements; CAT, catalase; CDDO, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid; CDDO-Me, 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid methyl ester; CI, confidence interval; CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; COX-2, cyclooxygenase-2; cPLA<sub>2</sub>, cytosolic phospholipase A<sub>2</sub>; CTGF, connective tissue growth factor; CVD, cardiovascular disease; 15d-PGJ<sub>2</sub>, 15-deoxy-D12,14-prostaglandin J<sub>2</sub>; ENaC, epithelial sodium channel; EndMT, endothelial-to-mesenchymal transition; E3RSI $\kappa$ B, E3 ubiquitin-ligases; ERKs, extracellular signal-regulated kinases; FBS, fetal bovine serum; fMLP, N-formyl methionyl-leucylphenylalanine; G-CSF, granulocyte colony-stimulating factor; GSH, glutathione; GSTs, glutathione S-transferases; HDM, house dust mite; HO, heme oxygenase; ICAM-1, intercellular adhesion molecule-1; IHD, ischaemic heart disease; I $\kappa$ B, inhibitory  $\kappa$ B; IL-1 $\beta$ , interleukin-1 $\beta$ ; NLRP3, Nod-like receptor with pyrin domain containing 3; NQO1, NAD(P)H: quinone oxidoreductase 1; JNKs, c-Jun NH2-terminal kinases; Keap1, Kelch-like ECH associated protein 1; KPF, kaempferol; LPS, lipopolysaccharide; LTA, lipotechoic acid; LTB<sub>4</sub>, leukotriene B<sub>4</sub>; MAPKs, mitogen-activated protein kinases; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MMP, matrix metalloproteinase; NF- $\kappa$ B, nuclear factor- $\kappa$ B; NO, nitric oxide; Nox, NADPH oxidase; Nrf2, NF-E2-related factor 2; OA, oleanolic acid; OVA, ovalbumin; PARP, poly(ADP-ribose) polymerase; PPARs, peroxisome proliferator-activated receptors; PKC, protein kinase C;

Pris, pristimerin; ROS, reactive oxygen species; Sal, salivarnolic acid; SGK1, serum and glucocorticoid-induced kinase-1; SOD, superoxide dismutase; Ssa, saikosaponin A; TAK1, TGF- $\beta$ -activated kinase 1; TGF, transforming growth factor; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; TSMCs, tracheal smooth muscle cells; TLR, Toll-like receptor; TZDs, Thiazolidinediones; VCAM-1, vascular cell adhesion molecule-1.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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