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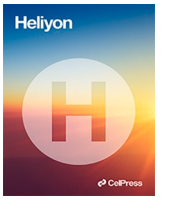

Review article

# The role of Keap1-Nrf2 signaling pathway in the treatment of respiratory diseases and the research progress on targeted drugs

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ABSTRACT

Lungs are exposed to external oxidants from the environment as in harmful particles and smog, causing oxidative stress in the lungs and consequently respiratory ailment. The NF-E2-related factor 2 (Nrf2) is the one with transcriptional regulatory function, while its related protein Kelch-like ECH-associated protein 1 (Keap1) inhibits Nrf2 activity. Together, they form the Keap1-Nrf2 pathway, which regulates the body's defense against oxidative stress. This pathway has been shown to maintain cellular homeostasis during oxidative stressing, inflammation, oncogenesis, and apoptosis by coordinating the expression of cytoprotective genes and making it a potential therapeutic target for respiratory diseases. This paper summarizes this point in detail in Chapter 2. In addition, this article summarizes the current drug development and clinical research progress related to the Keap1-Nrf2 signaling pathway, with a focus on the potential of Nrf2 agonists in treating respiratory diseases. Overall, the article reviews the regulatory mechanisms of the Keap1-Nrf2 signaling pathway in respiratory diseases and the progress of targeted drug research, aiming to provide new insights for treatment.

## 1. Introduction

Respiratory system diseases are a common disease type affecting the human health. The lesions are concentrated mainly on lung tissue, trachea, and bronchi. The course of the disease is long, and patients have coughing with breathing difficulties. In severe cases, it may cause serious harm or even death of patients [1]. Common respiratory diseases include pulmonary fibrosis (PF), chronic obstructive pulmonary disease (COPD), asthma, lung cancer, and acute lung injury/acute respiratory distress syndrome (ALI/ARDS) [2,3]. The oxidative stress may be originated from external sources of toxic substances in the air, including particles, chemicals, and infectious biological stressors, and from endogenous sources, such as reactive oxygen species (ROS) from metabolic activities within cells [4–6]. When a lung tissue is constantly stimulated by oxidative stress sources, the oxidative-reduction balance of lung cells could

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be disrupted, and pathways that promote inflammation be activated, causing chronic inflammation in the lung tissue toward a respiratory system disease consequently [7]. The activation of the Keap1-Nrf2 signaling pathway could promote transcription of redox balance factors, detoxification enzymes, and other genes to safeguard cells against oxidative injury and inflammatory damage. The pathway is essential in regulating redox balance in the lungs for the treatment [8–10]. Being classified as a Cap 'n' Collar (CNC) group of proteins, Nrf2 is encoded by the *Nfe2l2* gene [11,12]. Nrf2 regulates largely the transcriptional activation of more than 500 genes that provide protection to cells and that controlled by Keap1 [13]. Keap1 is encoded by the *KEAP1* gene and categorized in the BTB (Broad complex, Tramtrack, Bric-á-brac)-kelch protein family. Structurally, it consists of mainly a BTB domain located at the N-terminus, a glycine repeat domain (DGR) located at the C-terminus, and an intervening region (IVR) connecting the two domains [14]. The cysteine residues on its domains are sensitive to the influence of ROS or covalent modification by electrophiles. The Keap1 protein in humans has 27 cysteine residues that are extremely sensitive to the redox state in cells. Therefore, Keap1 is as an important oxidative stress sensor in cells [15–17].

The Keap1-Nrf2 signaling pathway is a redox-responsive endogenous antioxidant defense module [18] and mediates the regulation of oxidative damage by modulating the interplay of Nrf2 and Keap1 [17]. Keap1 forms a binding to Nrf2 and inhibits its protein degradation under normal conditions. When an oxidative stress occurs, Keap1 would dissociate itself from Nrf2, promoting the accumulation of Nrf2 within nucleus [17,19,20]. Nrf2 combines small musculoaponeurotic fibrosarcoma (sMaf) in the nucleus to form a heterodimer, and subsequently attaches to antioxidant response element (ARE), which drives the transcription of factors that related to antioxidants for ARE-encoded genes, including superoxide dismutases (SOD), catalase, glutathione peroxidase (GPx), and so on. Additionally, it transcribes detoxification enzymes related to transcription, including glutathione S-transferase (GSTs), NAD(P)H quinone oxidoreductase 1 (NQO1), and γ-glutamylcysteine synthetase (γ-GCS), and so on. Ultimately, these processes help mitigate the inflammatory responses caused by oxidative stress [21,22]. Nrf2 can also regulate the activity and inflammatory response of immune cells via multiple pathways to restrain inflammatory factor generation, to enhance anti-inflammatory cell function, and to regulate immune cell polarization [23]. These mechanisms work jointly to protect the lungs from inflammatory damage.

Thus, therapeutic strategies aiming at the Keap1-Nrf2 signaling pathway show great potential in treating respiratory diseases. By reducing intracellular ROS levels, the pathway helps to alleviate oxidative stress-induced cellular inflammation and restore oxidation-reduction homeostasis in the lungs. As a result, it can mitigate inflammatory lung damage and promote the expression of antioxidant factors and detoxification enzymes, and thus slow down the deterioration of respiratory diseases (Fig. 1) [19,20].

In recent years, the development of many active substances targeting the Keap1-Nrf2 signaling pathway has become a hotspot in drug development for respiratory diseases, and the main categories that have been studied so far include natural plant polyphenols [24], such as resveratrol [25], curcumin [26], quercetin [27], catechins [28], and so on; sulfur-containing compounds such as isothiocyanates [29]; selenium-containing compounds such as organoselenium compounds [30]; and heavy metals [31]. These compounds act on the Keap1-Nrf2 signaling pathway in two main ways. One way is to enhance Nrf2 accumulation and nuclear translocation by disrupting its binding with Keap1 through oxidative or alkylation modifications or competitive binding [32–34]. The other way is to promote the dissociation of Keap1 from Nrf2 by increasing Nrf2 phosphorylation [35]. No clinical trials are currently

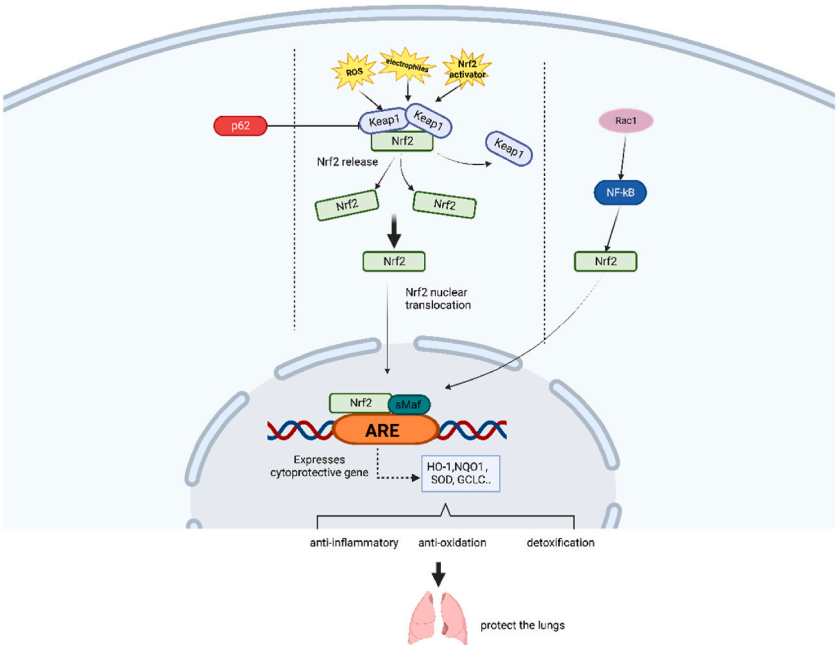



**Fig. 1.** The Keap1-Nrf2 signaling pathway protects the lung against oxidative stress and inflammatory responses. HO-1, NQO1, SOD, and GCLC are the downstream antioxidant target genes of Nrf2.
**Abbreviations**: HO-1: heme oxygenase 1; GCLC: glutamate-cysteine ligase catalytic subunit gene.

made on these active substances. Therefore, clinical trials are needed before medications targeting the Keap1-Nrf2 pathway can be marketed for the treatment of respiratory diseases.

In this study, a comprehensive analysis was carried out on the regulatory role of the Keap1-Nrf2 signaling pathway in respiratory diseases, to establish a theoretical foundation for the research and development of targeted therapeutic drugs.

## 2. The function of Keap1-Nrf2 signaling pathway in respiratory diseases

In this chapter, we will examine the crucial role of the Keap1-Nrf2 signaling pathway in respiratory diseases. Fig. 2 outlines the key mechanisms by which this pathway regulates various respiratory conditions, including PF, COPD, asthma, lung cancer, and ALI/ARDS.

### *2.1. Pulmonary fibrosis*

Pulmonary Fibrosis (PF) is a chronic and lethal respiratory illness that involves extensive and gradual reorganization of the lung tissue, leading to the accumulation of extracellular matrix, permanent scarring, and eventually impaired lung function and respiratory insufficiency [36]. At present, research has demonstrated that oxidative stress is the key driver in PF for inflammatory response, collagen deposition, and tissue fibrosis, and thus it is the main cause of PF development [37–39]. Keap1-Nrf2 signaling pathway is a crucial system of cellular protection against illness induced by oxidative stress. Once the pathway is activated, Nrf2 could be relocated to the nucleus, which prompts the transcription of various antioxidant genes, leading to a decrease in cellular damage caused by ROS, and playing a critical role in regulating PF [40]. Furthermore, Nrf2 is involved in modulating the expression of cytokines that are linked to inflammation.

Kikuchi et al. [41] confirmed the function of Nrf2 in preventing PF worsening in an immunodeficient mice model. They found that Nrf2 activated antioxidant response genes, enhanced the antioxidant capacity of lung tissue, reduced the damage caused by oxidative stress, and thereby protected lung tissue from further damage. Furthermore, Nrf2 can maintain the balance between Th1 and Th2 cells in the immune system, in which Th1 cells release cytokines that boost cell-mediated immune responses, while Th2 cells release cytokines that mainly regulate humoral immune responses and can sometimes reduce inflammation. However, an overactivated Th2 response may worsen the inflammation and fibrosis. Luckily, Nrf2 can regulate the Th1-Th2 balance and reduce the degree of inflammation and fibrosis by depressing the activation of Th2 cells but enhancing the activation of Th1 cells. These results provide important clues for further research on the possible use of Nrf2 in the treatment of PF.

Autophagy is a natural process of cleanup of damaged cells by devouring intracellular proteins or organelles, and using lysosomes to degrade devoured materials that is closely related to PF [42]. p62 is a well-known receptor for selective autophagy, and can compete with Keap1 in the binding to Nrf2, in which p62 removes Keap1 within autophagosome, halts Keap1-mediated degradation of Nrf2, and finally activates the Nrf2 pathway [43]. Dong et al. [44] established a bleomycin (BLM)-induced PF model in mice and intervened it with autophagy inhibitors and autophagy activators, and found that the alveolar structures of the PF mice were disrupted. The activation of autophagy can partially restore the alveolar structural damage induced by BLM and enhanced the expression of proteins that are associated with the Keap1-Nrf2 signaling pathway. In PF mice, autophagy-associated proteins MAP1LC3 (LC3) and Beclin 1

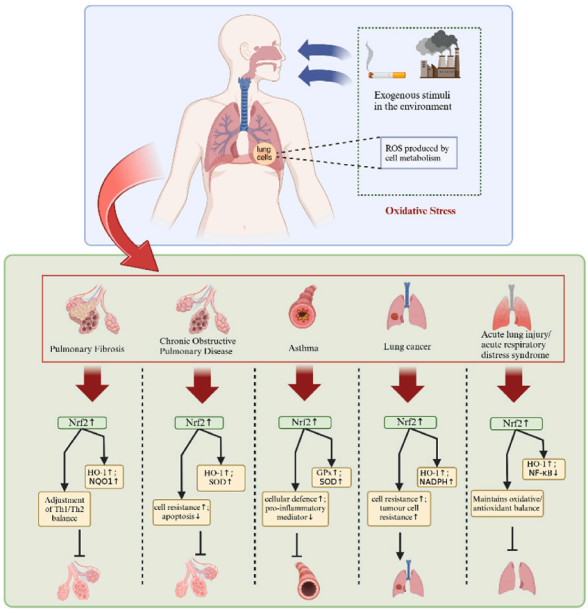



**Fig. 2.** The relationship between Keap1-Nrf2 pathway and respiratory diseases.
↑: increase; ↓: decrease; ⊥: inhibition.

were decreased and the p62 expression was increased. The activation of Keap1-Nrf2 pathway could regulate ROS-mediated autophagy and apoptosis, in which p62 could maintain the feedback loop of Keap1-Nrf2 [43], promote antioxidant response to autophagy, reverse the deleterious effects of overwhelming oxidative stress, and ultimately delay the deterioration of PF [45]. In addition, Liu et al. [46] confirmed the existence of an important signaling axis between Nrf2 and LOC344887, which plays a significant role in inhibiting PF. Activating the Nrf2-LOC344887 signaling pathway can effectively reduce collagen deposition, inflammatory response, and the degree of PF. This study provides strong evidence to support crucial function of Nrf2 in the treatment of PF.

### 2.2. Chronic obstructive pulmonary disease

Chronic Obstructive Pulmonary Disease (COPD) is a chronic inflammatory lung disease with alveolar wall damage and irreversible airway obstruction, causing high morbidity and mortality [47]. COPD is a smoking-induced disease whose development is associated with inflammation, protease/antiprotease imbalance, and oxidative stress [48]. COPD is predominantly identified by persistent inflammation of the minor air passages and degeneration of the lung tissue (emphysema) [49], in which oxidative pressure and inflammatory reactions are the main causes in the pathology of COPD [50]. Inhalation of cigarette smoke (CS) could stimulate the release of various inflammatory mediators from airway epithelium cells and macrophages at lung tissue surface, build up lung cells to a chronic inflammatory condition, and finally result in chronic inflammation of the airways [51]. Consequently, ROS could be generated in the lungs by inflammatory cells via metabolism, which exacerbates oxidative stress in COPD patients' lungs and furthermore destruct the alveoli and emphysema. In addition, ROS can aggravate the disease via systemic oxidative stress, andeventually the outbreak of pulmonary heart disease and respiratory failure would occur [52].

It is widely believed that the Keap1-Nrf2 signaling pathway plays a crucial role in reducing inflammation and oxidative stress caused by CS and may become an important therapeutic target to slow the development of COPD [53]. Isorhamnetin (Iso) is a class of flavonoid compounds having anti-inflammatory and antioxidant properties [54]. Xu et al. [55] showed that Iso could relieve airway inflammation. They detected Keap1 and Nrf2 expression levels in lung tissue of mice with CS-induced COPD using bronchoalveolar lavage fluid (BALF), and found that Iso could down-regulate Keap1 expression and up-regulate Nrf2 protective downstream factors, such as HO-1 and SOD, which reduced the pro-inflammatory effect of ROS, suppressed cytokine secretion that induces inflammation, activation of anti-inflammatory cytokines, and ultimately, alleviated the airway inflammation in COPD patients. Additionally, Iso can inhibit the nuclear factor kappa-B (NF-κB) activity and attenuate the inflammatory response, and alleviate of CS-induced airway inflammation and airflow limitation. NF-κB can regulate the inflammation by controlling the expression of various inflammatory factors [56]. Tan et al. [57] found that andrographolide could play anti-inflammatory effects through p62 by breaking up the Keap1-Nrf2 binding and up-regulating Nrf2 expression of HO-1 and NQO1, which could strengthen the antioxidant defense system; in addition, andrographolide promoted CS-induced apoptosis to the lung from chronic inflammation, which confirmed that andrographolide can act as an effective anti-inflammatory and antioxidant agent against COPD, and that this mode of action can be achieved precisely by activating the signaling pathway involving Keap1 and Nrf2.

Rangasamy et al. [48] found that in mice models, Nrf2 gene deletion could lead to early onset of emphysema and more severe damage, accompanied by more obvious manifestations of oxidative stress, inflammatory response and apoptosis. Iizuka et al. [58] also confirmed that Nrf2 had a protective effect on the progression of emphysema, in which Nrf2-knockout mice were more sensitive to CS-induced emphysema, showing increased pneumonia and permeability damage. After 8weeks of smoke exposure, neutrophil elastase activity in Nrf2 knockout mice was significantly enhanced, while pathological abnormalities were not detected in wild-type mice. Additionally, Nrf2 knockout mice lacked the inducible expression of regulated neutrophil elastase inhibitors and the activation of antioxidant/anti-inflammatory genes controlled by ARE. These findings may explain the increased susceptibility of Nrf2 knockout mice to developing neutrophilic inflammation. Ishii et al. [59] further confirmed that the responsiveness of the Nrf2 signaling pathway plays a vital role in the development of emphysema.

The above-mentioned findings suggest that the Nrf2 signaling pathway represents a promising therapeutic target that can prevent or reduce the development of COPD caused by smoking by enhancing antioxidant capacity and inhibiting inflammatory responses.

### 2.3. Asthma

Respiratory symptoms of asthma consist of persistent airway inflammation and reversible airflow obstruction. Inflammation stimulates the airway to act strongly against allergens or infectious agents. Symptoms of asthma include difficulty breathing, coughing, and wheezing [60]. Corticosteroid, commonly referring to glucocorticoid, have a wide range of anti-inflammatory effects, and are the first-line treatment drugs for treating asthma symptoms [61]. ROS can damage the glucocorticoid receptor signaling pathway, thus decreasing the sensitivity of asthmatic patients to corticosteroid and persistent airway inflammation or airflow obstruction [61]. Lung cells of asthma patients produce a large amount of ROS, which triggers severe oxidative stress, and exacerbates airway inflammation and insensitivity to corticosteroid, leading to poor asthma treatment [22]. To be effective in reducing airway inflammation, corticosteroid require a balanced redox environment [62]. Therefore, to restore lung redox balance and regain corticosteroid sensitivity, activating the Keap1-Nrf2 signaling pathway shall be potential and promising for asthma treatment.

Asthma is a disease of complex inflammation. During an asthma attack, accumulation of proteins in the extracellular matrix (ECM) and excessive mucus secretion in the lung cells of patients can cause mucus obstruction and airflow obstruction, generating more severe asthma phenotypes [63]. Casticin is a polymethylated flavonoid compound isolated from Fructus Viticis (the fruit of *Vitex rotundifolia*), which has anti-inflammatory activity, and can alleviate lipopolysaccharide(LPS)-induced lung injury [64]. Wang et al. [65] studied the impact of casticin on asthma by analyzing the expression of various inflammatory factors, including interleukin (IL)-6,

IL-8, MUC5AC, type I collagen, and fibronectin, in lipopolysaccharide-induced human lung bronchial epithelial cells (16-HBE) after treatment. They found that the expression of all these factors decreased after casticin treatment, and the inflammation and mucus obstruction of 16-HBE cells were reduced. They also found that casticin down-regulated the transcription of Keap1 and up-regulated the transcription of Nrf2. Additionally, the protein level of p-p65 decreased, which suggests that NF-κB expression was suppressed. Since 1970s, ketamine has been used as an anesthetic. Recent studies have found that it plays a role in treating inflammation, cell apoptosis, oxidative stress, and immune system regulation [66,67]. To further investigate the potential use of ketamine in alleviating asthma, Xiao et al. [68] detected the expression of oxidative damage biomarker MDA and antioxidant SOD and GPx, and the degree of Nrf2 protein expression in the lung tissue of mice model with mixed cell type asthma. They discovered that the MDA levels in the lungs of asthmatic mice increased, accompanied by high levels of oxidative stress and damage to apoptotic inflammatory cells. After treatment with ketamine, Nrf2 was up-regulated and the expression of SOD and GPx increased. Asthma syndromes such as airway hyperresponsiveness, mixed granulocytic airway inflammation, and excessive mucus generation were reduced. The alleviating symptoms disappeared after injecting Nrf2 inhibitor ML385.

Rangasamy et al. [69], it was found that Nrf2 gene deletion caused severe allergic reaction-driven airway inflammation and hyperresponsiveness in mice. Compared with wild-type mice, Nrf2-deficient mice displayed more significant mucous cell hyperplasia and eosinophil infiltration in the lungs after ovalbumin sensitization and stimulation. Furthermore, deletion of Nrf2 led to elevated expression of the T helper type 2 cytokines IL-4 and IL-13 in BALF and spleen cells after allergen stimulation. Disruption of the Nrf2 pathway reduced the antioxidant status of the lung and significantly attenuated the transcriptional activation of antioxidant genes, thereby exacerbating the severity of the asthma response. This finding suggests that the sensitivity of Nrf2-regulated antioxidant pathways could be a key factor in determining vulnerability to allergen-induced asthma. Oxidative stress is crucial in the development of asthma, with significant effects on airway epithelial cells and interactions between innate and adaptive immune cells [70]. Sussan et al. [70] showed that Nrf2-deficient mice were more susceptible to asthma, as evidenced by increased levels of oxidative stress, inflammation, mucus production, and airway hyperresponsiveness (AHR). Therefore, activating Nrf2 in airway epithelial cells can alleviate the onset of allergic asthma, and improving airway epithelial cell function to increase tight junction protein levels is one of the mechanisms by which Nrf2 reduces allergic asthma.

### 2.4. Lung cancer

Among all cancers, lung cancer has one of the highest mortality rates and is one of the most common malignant tumors [71,72]. As The Cancer Genome Atlas (TCGA) detection data demonstrate, the Keap1-Nrf2 signaling pathway undergoes frequent alterations in both lung adenocarcinoma and lung squamous cell carcinoma (SqCC), suggesting that there is a dysregulation of this pathway in lung cancer [73]. In cancer cells, the Keap1-Nrf2 signaling pathway can regulate various enzymes involved in gene-targeted antioxidant and detoxification pathways, including but not limited to HO-1, NQO1, GSTs, and SOD. Activation of these enzymes can enable cancer cells to adapt to harsh microenvironments, radiation, and chemotherapy, and alleviate endogenous oxidative stress [74].

The dysregulation of cancer cell migration can cause cancer metastasis, which is the main cause of poor prognosis in cancer patients. Therefore, cell migration plays a critical role in many human diseases, including cancer [75]. To explore the regulation of cell migration in the Keap1-Nrf2 signaling pathway, Ko et al. [76] used cell lines from non-small cell lung cancer (NSCLC) to measure cell migration. In NSCLC cells treated with the Nrf2 pathway inhibitor brusatol, the expression of Nrf2 was down-regulated, by which the migration and invasion of cell lines were inhibited and cell contraction was controlled. In addition, they detected the expression of Keap1 and Nrf2 using RT-qPCR and Western blot, as well as actin RhoA and Rho-related kinase ROCK1 protein. The results indicate that overexpression of Nrf2 led to an increase in the protein expression levels of RhoA and ROCK1. However, after brusatol inhibition, the activity of Nrf2 continued to decrease, indicating that the Keap1-Nrf2 signaling pathway may regulate the migration and invasion of NSCLC cells by controlling the RhoA-ROCK1 pathway.

Although the Keap1-Nrf2 signaling pathway is crucial for lung cancer progression, prolonged Nrf2 activation in cancerous cells may have detrimental effects [77]. The excessive activation of Nrf2 could give rise to excessive expression of multidrug resistance-associated protein 1 (MRP1), which may increase the multidrug resistance of cells, and increase the resistance and tumorigenic activity of cancer cells, resulting in poor prognosis for lung cancer [78]. Therefore, the overexpression of Nrf2-mediated MRP1 could be a direct indication of treatment resistance in the case of lung cancer.

In addition, studies have found that NSCLC patients with *KEAP1/NFE2L2* mutations have a shorter median overall survival [79]. Chian et al. [80] showed that in NSCLC, the activation of the Nrf2 signaling pathway is closely related to drug resistance. Highly expressed Nrf2 can lead to accelerated proliferation of tumor cells and resistance to chemotherapy drugs. Therefore, interfering with the Nrf2 pathway may help overcome drug resistance in NSCLC.

Recent clinical studies have found that Nrf2 can enhance the immune surveillance of damaged cells by promoting the transcription of a subset of genes associated with the senescence-associated secretory phenotype (SASP) [81]. This mechanism is termed the Nrf2-induced secretory phenotype (NISP). Baird et al. [82] found that to overcome the negative selective pressure exerted by NISP-mediated immune surveillance, malignantly Nrf2-activated cancers undergo significant immune editing to reduce their immunogenicity, which resulted in the inability of cytotoxic T cells and other immune surveillance effector cells to accurately recognize these Nrf2-activated cells as cancer cells, thereby accelerating their malignant progression and leading to poorer patient prognosis. Therefore, Nrf2 activation could not only increase resistance to chemotherapy but also lead to resistance to immune checkpoint inhibitors, which is inconsistent to all current treatment strategies [83], thereby finding new clinical treatment strategies targeting Nrf2 is demanded.

### 2.5. Acute lung injury/acute respiratory distress syndrome

Acute lung injury/acute respiratory distress syndrome (ALI/ARDS) is the main cause of respiratory failure, posing as one of the most challenging issue in clinical practice. It is identified by the activation of pro-inflammatory and oxidative pathways, causing a rapid and strong inflammatory response, leading to neutrophil accumulation, interstitial edema, and alveolar epithelial damage in lung tissue, which in turn leads to lung ECM remodeling [84,85]. ALI is an acute inflammatory disease and a milder form of ARDS. Numerous studies have demonstrated that infection from Gram-negative bacteria plays a main role in the development of ALI, in which LPS, a key constituent of Gram-negative bacterial outer membranes, can induce lung damage and an inflammatory reaction [86]. Inhibiting the Keap1-Nrf2 pathway is a feasible approach to reduce oxidative stress and related inflammation, showing application potential in the treatment of ALI/ARDS [87].

Li et al. [88] found that panaxydol (PX) extracted from ginseng roots showed potential therapeutic effects on LPS-induced ALI in mice. Being treated with PX, the mice were protected from LPS-induced ALI, showing significant improvement in lung pathology and reduction in pulmonary edema, inflammation, and ferroptosis. Ferroptosis is categorized as a form of regulated necrosis, which is more immunogenic than apoptosis, and is potential to push the development of ALI. In vitro experiments demonstrated that PX exhibited an inhibitory effect on the BEAS-2B cells from bronchial epithelial cell line and was able to diminish ferroptosis and inflammatory responses induced by LPS. Subsequent studies revealed a connection between ferroptosis and inflammation, and found that ferroptosis mediated the onset of inflammation in LPS-treated BEAS-2B cells. PX may improve the inflammatory response induced by LPS by inhibiting the ferroptosis process. In addition, PX also exhibits its anti-inflammatory effect by inhibiting ferroptosis by upregulating the Keap1-Nrf2/HO-1 pathway.

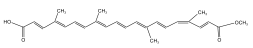
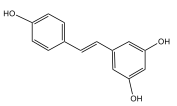
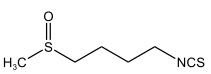
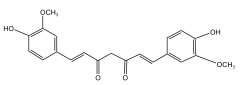
NXPZ-2 is a naphthylsulfonamide derivative. Zhang et al. [89] demonstrated that NXPZ-2 was able to effectively block the Keap1-Nrf2 protein-protein interaction (PPI). In a structure-based molecular hybridization strategy, by using NXPZ-2 and Nrf2 activator sulforaphane(SFN), they designed a series of new compounds containing naphthalenesulfonamide with isothiocyanate groups, including thioethers, sulfites, and sulfonyl groups. Molecular docking studies further elucidated the distinct activities of naphthylsulfonamide compounds containing thioether, sulfite, and sulfonyl groups. Among these novel compounds, SCN-16 exhibited a good inhibitory KD2 value (0.455 mM) against PPI. In the peritoneal macrophage model stimulated by LPS, SCN-16 notably enhanced the nuclear accumulation of Nrf2 protein, diminished its cytoplasmic presence, and consequently elevates the levels of the protective enzymes HO-1 and NQO-1 downstream, exhibiting a superior efficacy compared to NXPZ-2 and SFN. In addition, SCN-16 can also suppress the generation of ROS and NO, and decrease the level of the pro-inflammatory cytokine known as tumor necrosis factor-α (TNF-α). In a rodent model of ALI caused by LPS, SCN-16 significantly reduced the inflammatory reaction and pulmonary damage triggered by LPS by enhancing the nuclear migration of Nrf2. The above-mentioned findings indicate that SCN-16 is a promising candidate of new compound aiming at the Keap1-Nrf2 protective pathway in the clinical management of ALI.

## 3. Targeted therapy drugs

Keap1-Nrf2 signaling pathway activation is initiated by oxidative damage. After activation, it regulates oxidative levels and maintains cellular homeostasis by transcribing antioxidant target genes, showing good preventive and therapeutic effects in the pathology of ROS-mediated respiratory diseases [90]. Currently, many compounds have potential to reduce the severity of respiratory diseases by activating the Nrf2 pathway (Table 2) [91]. Therefore, activation of the Keap1-Nrf2 signaling pathway through Nrf2 activators has become a potential hot spot for the development of new respiratory disease drugs.

Among them, the modes of action of Nrf2 activators are divided into covalent activation and non-covalent activation [92].

**Table 1**
Nrf2 covalent activator binding targets to Keap1.

| Compound | Chemical structure | Cysteine residues targeted | References |
|---|---|---|---|
| Bixin |  | Cys151 | [98] |
| RSV |  | Cys151, Cys257, Cys273, Cys288 and Cys297 | [100] |
| SFN |  | Cys38, Cys151, Cys368, and Cys489 | [103] |
| Curcumin |  | Cys151 | [104] |

### 3.1. Covalent activation of Nrf2

The cysteine amino acid residues in Keap1 are the main targets of covalent activators that interact with Keap1, causing a conformational change that dissociates Keap1 from Nrf2 and activates Nrf2 to exert cellular protective effects [93]. Drugs that act on the cysteine residues of Keap1 are mainly oxidizing phenols and quinones, polyenes, hydrogen peroxide, isothiocyanates, and inducers related to Michael reaction receptor molecules, such as curcumin, cinnamic acid derivatives, carnosol, flavonoids, terpenoids, and

**Table 2**
Promising small molecule compounds for future development of respiratory diseases.

| Small Molecule Compounds | Respiratory Diseases | Effects | References |
|---|---|---|---|
| EGCG | PF | Enhanced antioxidant activity and phase II enzymes via the Keap1-Nrf2 signaling pathway and inhibition of inflammation during bleomycin-induced PF. | [111] |
| Tan IIA | PF | Tan IIA inhibits silica-induced EMT and TGF-β1/Smad signaling in lung cells by activating the Keap1-Nrf2 signaling pathway and antioxidants. | [112] |
| | PF | Tan-IIA activates the Sesn2/Keap1-Nrf2 signaling pathway, up-regulating the expression of the antioxidant gene Sesn2, which helps restore redox homeostasis and inhibits myofibroblast activation in PF. | [113] |
| Pts | PF | Protection against early PF after acute lung injury through activation of the Keap1-Nrf2 signaling pathway, inhibition of caspase-dependent, A20/NF-κB, and NLRP3 signaling pathways, and regulation of oxidative stress, apoptosis, and inflammatory responses. | [107] |
| Vit U | PF | Vit U supplementation protects against VPA-induced tissue damage by activating the Keap1-Nrf2 antioxidant system and improving Nrf2 activity in the lung under oxidative stress, enhancing antioxidant capacity. | [109] |
| Bixin | PF | Blocking Keap1-mediated Nrf2 degradation activates Nrf2 signaling, thus reducing inflammatory cell accumulation, and improving lung inflammation and fibrosis. | [97] |
| PCB | PF | Reducing oxidative and inflammatory cell damage through the Keap1-Nrf2-HO-1 pathway, thereby alleviating PF symptoms. | [114] |
| DHQ | COPD | DHQ significantly reverses CS-induced iron death in vivo and in vitro via an Nrf2-dependent signaling pathway. | [115] |
| Iso | COPD | Iso significantly attenuates CS-induced inflammatory responses in COPD mice by affecting the Keap1-Nrf2 pathway. | [55] |
| Gbs | COPD | Gbs inhibits CS-induced oxidative stress and inflammatory responses in COPD rats via the Nrf2 pathway. | [116] |
| Curcumin | COPD | The covalent binding of curcumin to Keap1 promotes the synthesis and restoration of GSH, enhancing the redox sensing capability of Nrf2. | [117] |
| Eda | Asthma | Probably, through the activation of the Keap1-Nrf2 pathway and HO-1, it achieves anti-inflammatory and antioxidant effects, resulting in anti-asthmatic actions. | [118] |
| NEI | Asthma | NEI activates the Keap1-Nrf2 pathway, promoting the release of antioxidant factors, enhancing antioxidant enzyme activity, and finally improving symptoms in obese asthmatic rats. | [119] |
| RSV | Asthma | RSV activates the Keap1-Nrf2 antioxidant defense system to protect against oxidative stress in a rat model of obesity-asthma. | [99] |
| Ketamine | Asthma | Ketamine alleviates asthma symptoms by activating the Keap1-Nrf2 signaling pathway to reduce oxidative stress and neutrophil airway inflammation. | [68] |
| Casticin | Asthma | Casticin induces the Keap1-Nrf2 signaling pathway and inhibits the NF-κB pathway in 16-HBE cells. | [65] |
| TRIM protein | Lung cancer | TRIM15 plays a critical role in promoting NSCLC progression by elevating Keap1 ubiquitination and degradation-mediated Nrf2 stability. | [120] |
| Nestin | Lung cancer | The ESGE motif of Nestin interacts with Keap1's Kelch domain, and competes with Nrf2 for binding, which prevents Nrf2 from being degraded by Keap1 and increase the generation of antioxidant enzymes that regulate cellular redox balance and enhance resistance to oxidative stress in NSCLC. | [121] |
| BRD4 | Lung cancer | BRD4 binds to the Keap1 promoter, activating its transcription and reducing Nrf2 stability in SCLC. It also binds to Nrf2 protein independently of Keap1, inhibiting Nrf2 activity and enhancing cellular resistance to oxidative stress. | [122] |
| ZJ01 | ALI/ARDS | Successfully attenuated hyperoxic ALI in a mouse model via the Nrf2/HO-1 pathway. | [123] |
| SCN-16 | ALI/ARDS | SCN-16 significantly increases the Nrf2 protein in the nucleus, reduces the Nrf2 protein in the cytoplasm, and further increases the downstream protective enzymes HO-1 and NQO-1. It inhibits the production of ROS and NO, reduces the expression of the pro-inflammatory cytokine TNF-α, promotes Nrf2 nuclear translocation and significantly reduces LPS-induced inflammatory response and lung injury in ALI mice. | [89] |
| PX | ALI/ARDS | PX upregulated the Keap1-Nrf2/HO-1 pathway against ferroptosis, and demonstrated its anti-inflammatory effect. | [88] |
| SIT | ALI/ARDS | SIT regulates oxidative stress and autophagy through the p62-Keap1-Nrf2 signaling pathway and has the potential to treat SAP-ALI. | [87] |
| LCB | ALI/ARDS | LCB improves the levels of oxidative stress and inflammatory markers through the Keap1-Nrf2 signaling pathway. | [124] |
| HD | ALI/ARDS | HD alleviates LPS-induced oxidative stress and inflammation in ALI through the MAPK/NF-κB and Keap1-Nrf2/HO-1 pathways. | [125] |

**Abbreviations**: EGCG: Epigallocatechin-3-gallate; EMT: epithelial-mesenchymal transition; Iso: isorhamnetin; PCB: phycocyanin; Eda: edaravone; NEI: neutrophil elastase inhibitors; RSV: resveratrol; TRIM: the tripartite motif; BRD4: bromodomaincontaining protein 4; SIT: sitagliptin; SAP-ALI: severe acute pancreatitis-related acute lung injury; LCB: Licochalcone B; HD: Hydnocarpin D.

other compounds [92,94]. Table 1 summarizes the cysteine residue targets of Keap1 that covalently bind with Nrf2 activators.

Characterized by a gradual onset of inflammation and fibrosis, particle-induced lung injury is a complex pulmonary disease. Lung injury caused by $SiO_2$ exposure is the most severe, ultimately leading to diffusion of PF, distortion of lung tissue structure, and respiratory failure [95,96]. Bixin is a carotenoid extracted from the seeds of *Bixa orellana*. In addition to its role as a colorant, it also possesses anti-inflammatory, anti-tumor, and antioxidant activities. Xue et al. [97] found that bixin could enhance Nrf2 expression in the lungs of mice with silica-induced fibrosis, mitigate the accumulation of inflammatory cells, and ameliorate pulmonary inflammation and fibrosis progression. Using an antioxidant gene expression array, they analyzed the mechanism and found that bixin could activate Nrf2 by blocking Keap1-mediated Nrf2 ubiquitination and degradation with the key sensor Cys-151 residue in Keap1, thereby realizing cellular protection [98].

Resveratrol (RSV) is a natural plant polyphenol with excellent antioxidant activity. Li et al. [99] demonstrated in experiment that RSV treatment could reduce serum lipid levels and decrease lung ROS production while increasing antioxidant enzyme activity in obese asthmatic rat models. The western blot analysis showed that RSV treatment could down-regulate the expression of Keap1 and up-regulate Nrf2 expression in rat cells. In addition, RSV could react with the cysteine residues of Keap1 (Cys151, Cys257, Cys273, Cys288 and Cys297) through oxidation or alkylation to dissociate Nrf2 from Keap1, express Nrf2 transcriptional antioxidant genes, and consequently achieve the therapeutic effect on asthma [100].

SFN is mainly derived from cruciferous vegetables and it possesses potent anti-cancer activity, anti-inflammatory, and antioxidant abilities [101]. Liu et al. [102] demonstrated through RNA-seq analysis that the long non-coding RNA LOC344887 is a novel Nrf2 target gene with anti-fibrotic properties, and can control genes and signaling pathways related to fibrosis. SFN can activate LOC344887 to achieve anti-PF functions. The mechanism may be associated with the increase of pulmonary Nrf2 activity by SFN through the modification of cysteine residues on Keap1 (e.g. Cys38, Cys151, Cys368, and Cys489) [103], up-regulation of the novel anti-fibrotic Nrf2 target gene LOC344887, and inhibition of N-cadherin (CDH2) and other fibrotic genes by SFN against fibrosis.

### 3.2. Non-covalent activation of Nrf2

The non-covalent blocking of Keap1-Nrf2 PPI causes release and activation of Nrf2, resulting in downstream effects [105]. This process can be referred to as the non-covalent activation of Nrf2.

Pterostilbene (Pts), a bioactive compound in blueberries, exhibits anti-inflammatory, antioxidant, and anti-fibrotic properties [106]. Yang et al. [107] found that in an LPS-induced PF mice model, Pts could inhibit the expression of NADPH oxidase 4(NOX4) and Keap1, activate Nrf2, and transcribe downstream antioxidant target genes of Nrf2, after which the degree of fibrosis in PF mice was alleviated. NOX4 is an oxidase expressed mainly in lung tissues. Using molecular docking and dynamic simulation, a computational study [108] discovered that Pts interacted directly with the basic amino acids situated within the DGR segment of Keap1, causing the breakdown of Keap1-Nrf2 PPI and thereby regulating Nrf2 activation. Therefore, the ability of Pts to inhibit Keap1-Nrf2 PPI has opened the door for the development of targeted medications for the treatment of PF.

Vitamin U (Vit U) is a novel free radical scavenger that can eliminate ROS in living organisms. Vit U has been shown to protect rats from suffering from propionic acid-induced lung damage. The mechanism is that the binding of ETGE motif in the Neh2 domain of Vit U and Nrf2 dissociates Nrf2 from the binding of Keap1-Nrf2, which up-regulates the expression of Nrf2 and restores lung redox homeostasis, finally reducing lung damage [109]. Therefore, by activating Nrf2, Vit U acts as a Keap1-Nrf2 PPI inhibitor to treat lung diseases effectively.

Lu et al. [110] used a head-to-tail loop strategy to create peptide Keap1-Nrf2 PPI inhibitors with high cellular activity. They adopted a basic sequence of acidic amino acids as a scaffold for the cyclic peptide and developed a suitable ligation strategy informed by the binding interaction between the peptide and Keap1. Incorporating glycine as a connecting element not only eliminated terminal charges but also enhanced the peptide stability and restricted the binding conformation, by which a new cyclic peptide 3 was created featuring a strong binding affinity for Keap1 and potent Nrf2 activation at the cellular level.

### 3.3. Clinical research

Some Nrf2 activators have currently entered the clinical validation stage. Table 3 summarizes them and their clinical validation

**Table 3**
Clinical validation of Nrf2 activators.

| Nrf2 activator | Clinical validation direction | Clinical validation phase | References |
|---|---|---|---|
| Bardoxolone methyl | Chronic kidney disease | Phase III | [130] |
| omaveloxolone | Friedreich's ataxia | Approval | [129] |
| Dimethyl fumarate | Relapsing-remitting multiple sclerosis (MS) and relapsing forms of MS | Approval | [131] |
| | Relapsed and refractory cutaneous T cell lymphoma | Phase II | [132] |
| SFN | Has entered multiple clinical trials for respiratory diseases and cancer | Most studies are in early stages, focusing on safety, dosage, and preliminary efficacy. | [126–128, 133] |
| Oltipraz | Focused on cancer prevention and liver disease treatment. | Phase II | [134] |

directions.

SFN, an isothiocyanate naturally present in cruciferous vegetables, is considered a potential drug for the treatment of airway inflammation due to its ability to induce Nrf2 expression [126]. However, as clinical studies showed, supplementation with SFN in healthy individuals failed to activate the expression of genes associated with antioxidants and did not prevent airway inflammation caused by neutrophils in a model of ozone exposure [126]. Similarly, Wise et al. [127] conducted a four-week experiment on treating COPD patients with SFN orally, the outcome indicated that SFN did not induce the activation of genes targeted by Nrf2 and had no significant effect on the levels of oxidative stress and airway inflammation markers. In a pulmonary function test at two different dose levels (25 and 150 μmoles), no significant differences were shown between SFN-treated group and placebo group. However, Brown et al. [128] found that the bronchoconstrictor response in certain types of asthma patients could be positively affected by ingesting SFN. Although the efficacy of SFN is not consistent in all asthmatic patients, SFN can significantly reduce the bronchoconstrictive effect of methacholine(MCh)-induced expiratory volume in 1 s (FEV1) in 60% of asthmatic patients.

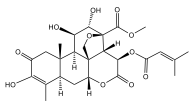
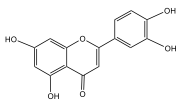
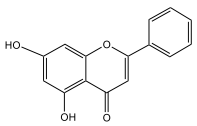
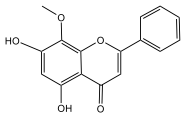
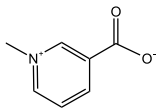
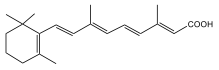
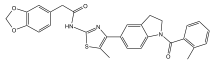
In 2023, the Nrf2 activator omaveloxolone received clinical approval for the treatment of Friedreich's ataxia, marking an important milestone in the clinical application of Nrf2 activators [129]. Omaveloxolone exerts antioxidant protective effects by activating Nrf2, making it a potential candidate for treating respiratory diseases.

### 3.4. Nrf2 inhibitors

The dual role of Nrf2 in cancer is widely recognized [135]. Normally, Nrf2 activation induces antioxidant gene expression, protecting cells from oxidative damage. However, in cancer, Nrf2 functions are complex. Moderate activation maintains normal cellular functions and prevents carcinogenic damage, while excessive activation in certain cancer cells enhances their survival and therapy resistance. This excessive activation of Nrf2 not only aids in tumor cell survival but also promotes their proliferation and metastasis [136]. Additionally, abnormal activation of the Nrf2 pathway has been shown to be closely associated with tumor aggressiveness and poor prognosis [137]. Therefore, targeting the abnormal activation of Nrf2, researchers have proposed developing of Nrf2 inhibitors as a potential anti-cancer therapeutic strategy. Table 4 summarizes the types of Nrf2 inhibitors and their effects on Nrf2 activity.

Currently, common Nrf2 inhibitors mainly include active substances such as alkaloids or flavonoids extracted from natural products, as well as compounds with Nrf2 inhibitory activity discovered through high-throughput screening such as ML385 [138]. Brusatol is the main biologically active natural quassin extracted from *Brucea javanica* [139]. Studies have shown that Brusatol can

**Table 4**
Nrf2 inhibitors and their effects on Nrf2 activity.

| Nrf2 inhibitors | Chemical structure | Mechanism | References |
|---|---|---|---|
| Brusatol |  | Combining Brusatol with cisplatin reduces Nrf2 and downstream protein expression, enhancing tumor cell DNA damage and apoptosis. | [141] |
| Luteolin |  | Luteolin downregulates the protein expression of Nrf2, HO-1, and Cripto-1. | [142] |
| Chrysin |  | Chrysin significantly reduced Nrf2 expression at both the mRNA and protein levels through down-regulating PI3K-Akt and ERK pathway. | [143] |
| Wogonin |  | In HepG2 cells, wogonin prevents Nrf2 nuclear translocation and promotes ROS-dependent cell death by reducing the activity of MRP. | [144] |
| Trigonelline |  | Trigonelline effectively reduced the basal and tBHQ-induced Nrf2 activity in all cell lines by decreasing the nuclear accumulation of Nrf2 protein and blocked the expression of Nrf2-dependent proteasome genes and proteasome activity. | [145] |
| All-trans retinoic acid (ATRA) |  | ATRA binds to transcription factors such as Nrf2 and prevents them from binding to ARE. | [146] |
| ML385 |  | ML385 can significantly reduce the expression of Nrf2 and its downstream target HO-1. | [138] |

enhance the sensitivity of various cancer cells to chemotherapy drugs by specifically blocking Nrf2 in vitro [140]. Ye et al. [139] found that Brusatol shows potent cytotoxic effects against various cancer cell lines, particularly in hepatocellular carcinoma (HCC). It inhibits cell viability, proliferation, and induces apoptosis in HCC cells. Brusatol activates autophagy in liver cell lines, with the autophagy inhibitor chloroquine reversing its effects on apoptosis in Bel7404 cells. Mechanistically, Brusatol inhibits the PI3K/Akt/mTOR pathway, which is crucial for cell survival and proliferation. It also suppresses invasion, migration, and EMT in HCC cells. In a human liver xenograft tumor model in nude mice, Brusatol significantly inhibited tumor invasion and proliferation. These findings underscore Brusatol as a promising anti-cancer drug candidate or adjunct to current chemotherapy for HCC treatment.

## 4. Outlook

The Keap1-Nrf2 signaling pathway functions as a crucial antioxidant defense mechanism, showing significant promise in preventing and treating respiratory diseases, making it a focal point in drug development for pulmonary conditions. Through comprehensive research and optimization of Nrf2 activators, it is anticipated that more efficacious new drugs will be developed for the treatment of respiratory diseases. Li et al. [147] applied molecular docking techniques and 3D-QSAR to assess the interaction of antioxidant phytochemicals with the Nrf2 binding site on Keap1, and screened for phytochemicals showing high binding affinity to Keap1, which provides a direction for the discovery of efficient activators regarding the Keap1-Nrf2 signaling pathway. Liu et al. [148] used simple mathematical models to assess the Keap1-Nrf2/ARE pathway quantitatively; for example, the quantitative assessment on the degree and magnitude of amplification of Nrf2 activation could help identify sensitive molecular targets in the pathway and break through the Keap1-Nrf2 mechanism crosstalk in vivo to develop drugs that more precisely regulate intracellular antioxidant levels.

Although the Keap1-Nrf2 antioxidant pathway has the potential to target various lung diseases, the activation of Nrf2 in lung cancer has a paradoxical role. Normal activation of Nrf2 protects normal cells from carcinogens. However, the increased expression of Nrf2 would cause resistance to chemotherapy and radiotherapy, and increase the invasiveness of lung cancer cells, triggering "Nrf2 addiction" and a malignant phenotype of cancer cells and resulting in poor prognosis of cancer patients [149]. Hence, pharmacologically targeting Nrf2 inhibition shall be a promising way for treating Nrf2-addicted lung cancer. Most of the currently known Nrf2 inhibitors have been developed from natural compounds such as flavonoids and alkaloids derived from plants, and some vitamins such as ascorbic acid and retinoic acid [150]. Difficulties of in vivo delivery and biotoxicity of natural plant compounds still limit the development process. The development of natural plant compound-based Nrf2 inhibitors can be accelerated by using materials such as nanoparticles and liposomes for encapsulation or modification, as well as further structural modifications on natural compounds.

In recent years, mammalian target of rapamycin (mTOR) has emerged as a crucial target in the investigation of cancer pathology. Activation of the mTOR pathway was found in NFE2L2 mutant lung cancer and was able to inhibit β-TrCP expression to promote Nrf2 nuclear translocation. Sapanisertib, an mTORC1/2 inhibitor and TAK-228 drug, shows promising therapeutic outcomes in treating squamous lung cancer patients with NFE2L2 gene mutations, although it is still in clinical trials. This suggests that a new generation of mTORC1 or mTORC2 inhibitors could be a novel approach to treating lung cancer. In addition, CRISPR technology can be used to screen for redox-deficient genes in Keap1-Nrf2 mutant lung cancer, as well as high-throughput drug screens to find relevant targeted therapeutics.

## 5. Conclusion

Inhibiting Nrf2 expression in the Keap1-Nrf2 signaling pathway or developing Nrf2 inhibitors is the key to treat respiratory diseases. In addition, deep exploration to the mechanism of action of various Nrf2 activators and inhibitors in the Keap1-Nrf2 signaling pathway is in great demand for new drugs designed specifically to treat respiratory illnesses. Active substances targeting the Keap1-Nrf2 signaling pathway have still a long way to go from clinical development and use. A thorough investigation of the intracellular functions of the Keap1-Nrf2 signaling pathway, taking into account all relevant influencing factors, will lay the foundation for new therapeutic approaches to treat respiratory diseases. This strategy is promising and deserves further study.

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## Data availability statement

No data was used for the research described in the article.

## CRediT authorship contribution statement

**Mengyang Zhang:** Writing – original draft. **Jing Wang:** Writing – original draft. **Runze Liu:** Formal analysis. **Qi Wang:** Formal analysis. **Song Qin:** Writing – review & editing. **Yuqin Chen:** Supervision. **Wenjun Li:** Writing – review & editing.

## Declaration of competing interest

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

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