

# Resveratrol as a potential therapeutic drug for respiratory system diseases

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**Abstract:** Respiratory system diseases are common and major ailments that seriously endanger human health. Resveratrol, a polyphenolic phytoalexin, is considered an anti-inflammatory, antioxidant, and anticancer agent. Thanks to its wide range of biological activities, resveratrol has become a hotspot in many fields, including respiratory system diseases. Indeed, research has demonstrated that resveratrol is helpful to relieve pulmonary function in the general population. Meanwhile, growing evidence indicates that resveratrol plays a protective role in respiratory system diseases. This review aimed to summarize the main protective effects of resveratrol in respiratory system diseases, including its anti-inflammatory, antiapoptotic, antioxidant, antifibrotic, antihypertensive, and anticancer activities. We found that resveratrol plays a protective role in the respiratory system through a variety of mechanisms, and so it may become a new drug for the treatment of respiratory system diseases.

**Keywords:** respiratory system diseases, resveratrol, inflammation, apoptosis, oxidation

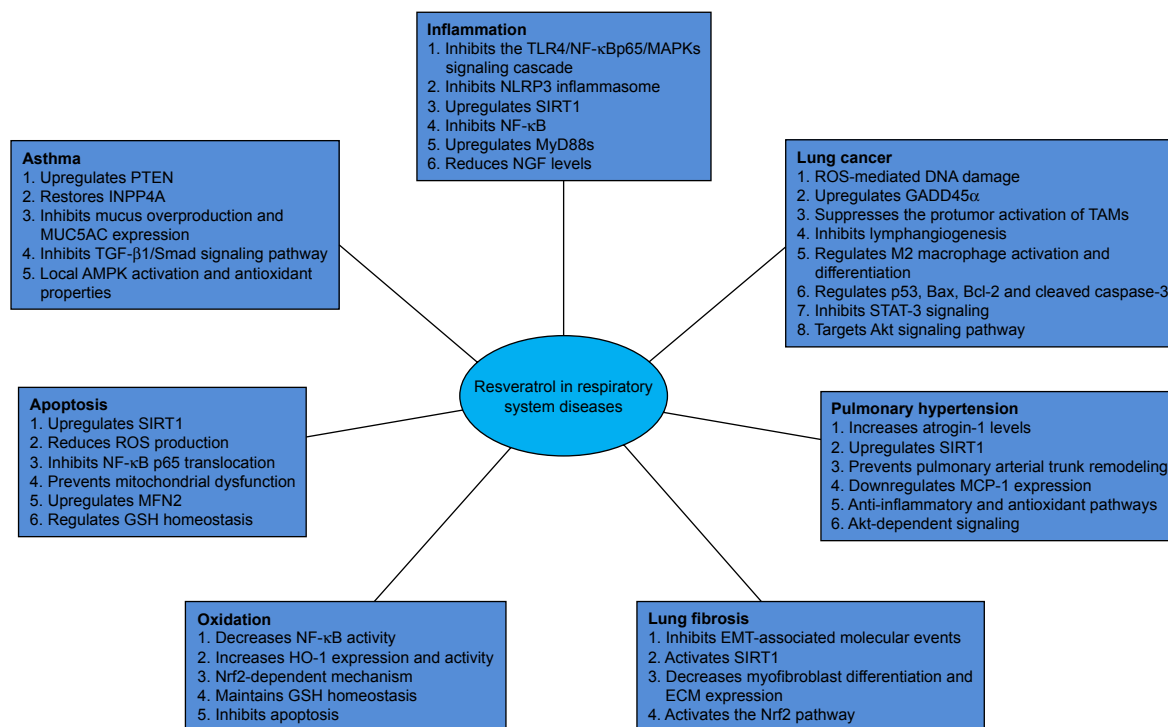
## Introduction

Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a polyphenolic compound found in multiple plant species, including grapes and peanuts. Its chemical structure comprises two aromatic rings connected by a methylene bridge; there are two isomeric forms, *cis* and *trans* isomers, of which the *trans* variant displays biological activities.<sup>1</sup> Resveratrol was first identified by Takaoka in *Veratrum grandiflorum* roots in 1939.<sup>2</sup> Later on, it was described as the "French paradox" in 1992, based on the notion that due to red wine consumption, the risk of cardiovascular disease in French individuals is lower than that of other Europeans despite the high intake of saturated fats.<sup>2,3</sup> In addition to alcohol, red wine contains many polyphenols, including resveratrol.<sup>4</sup> Multiple studies, including *in vitro* and animal experiments, have confirmed that resveratrol has protective effects on multiple tissues and organs.<sup>5-7</sup> This study reviews the potential effects of resveratrol in respiratory system diseases, from the aspects of inflammation, apoptosis, oxidation, fibrosis, pulmonary hypertension, and cancer, describing evidences for related molecular mechanisms (Figure 1).

## Anti-inflammatory effects

Inflammation is an innate protective response of the immune system, resisting external infection and tissue damage, assisting and promoting the recovery of tissue structures, and eliminating invasive pathogens.<sup>8</sup> However, excessive and uncontrolled inflammation causes severe tissue damage and secondary inflammation, and even DNA damage.<sup>8,9</sup> NF- $\kappa$ B, a regulator of the inflammatory process, is essential for maximal transcription of many cytokines that contribute to neutrophil infiltration in the lung.<sup>10,11</sup>

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**Figure 1** Protective mechanisms of resveratrol in respiratory system diseases.

**Abbreviations:** ECM, extracellular matrix; EMT, epithelial–mesenchymal transition; GSH, glutathione; ROS, reactive oxygen species; TAM, tumor-associated macrophages.

Therefore, functionally inhibiting NF- $\kappa$ B is considered a promising anti-inflammatory strategy. SIRT1, an NAD<sup>+</sup>-dependent protein deacetylase, modulates inflammatory responses by deacetylating histones in the promoter regions of downstream genes, including *NF- $\kappa$ B* and *AP-1*.<sup>12</sup> Resveratrol has protective effects on lipopolysaccharide (LPS)-induced inflammation in animal experiments. In the rodent model, resveratrol mitigates LPS-induced acute lung inflammation by inhibiting the TLR4/NF- $\kappa$ B/p65/MAPKs signaling cascade and NLRP3 inflammasome.<sup>13,14</sup> Resveratrol also alleviates the inhibitory effects of LPS on SIRT1 expression and inhibits LPS-induced activation of MAPKs and NF- $\kappa$ B both in vivo and in vitro.<sup>15</sup> Furthermore, resveratrol is helpful in alleviating spinal cord injury-induced inflammatory damage in the rat lung, by significantly decreasing neutrophil infiltration and the production of inflammatory mediators, upregulating SIRT1, and inhibiting NF- $\kappa$ B.<sup>16</sup> Moreover, resveratrol also reduces the production of inflammatory mediators in respiratory epithelial cells and the lung tissue of mice infected with nontypeable *Haemophilus influenzae*, by upregulating MyD88s, which is a negative regulator of the NF- $\kappa$ B-dependent inflammatory response.<sup>17</sup> Resveratrol inhibits airway hyperresponsiveness and persistent airway inflammation by reducing NGF levels in respiratory syncytial virus-infected mice.<sup>18</sup> Resveratrol triggers multiple

anti-inflammatory pathways to reduce lung injury caused by staphylococcal enterotoxin B in mice.<sup>19</sup> In preterm rats, resveratrol protects against hyperoxia-induced lung injury via its antioxidant, anti-inflammatory, and antifibrotic effects, promoting the transdifferentiation of alveolar type II epithelial cells into type I counterparts and suppressing Wnt/ $\beta$ -catenin signaling.<sup>20</sup> Furthermore, resveratrol was shown to attenuate hypoxia–reoxygenation-induced type II pneumocyte dysfunction, partially by promoting surfactant protein expression and suppressing inflammation via NF- $\kappa$ B pathway involvement.<sup>21</sup>

Asthma is one of the most common chronic inflammatory diseases worldwide, and it is characterized by airway inflammation, remodeling, and airway hyperresponsiveness. Interestingly, resveratrol significantly alleviates asthma by upregulating PTEN,<sup>22</sup> restoring INPP4A,<sup>23</sup> inhibiting mucus overproduction and MUC5AC expression,<sup>24</sup> and downregulating TGF- $\beta$ 1, inhibiting TGF- $\beta$ 1/Smad signaling and epithelial–mesenchymal transition (EMT) in an ovalbumin-induced murine model of asthma.<sup>25</sup> In a mouse model of house dust mite-induced asthma, the effects of resveratrol may be associated with Syk protein downregulation.<sup>26</sup> Another report demonstrated the protective effects of resveratrol in obesity-associated allergic airway inflammation in mice via local AMPK activation and antioxidant properties.<sup>27</sup>

## Antiapoptotic activities

Mounting evidence indicates that apoptosis dysregulation is involved in the pathogenetic mechanisms of multiple respiratory system diseases, including asthma, airway inflammation, acute lung injury (ALI), acute respiratory distress syndrome, pulmonary fibrosis, and lung cancer.<sup>28–31</sup> Reactive oxygen species (ROS) are natural byproducts of cellular metabolism, and induce cell death at excessive levels.<sup>32</sup> SIRT1 reduces ROS levels and promotes cell activity.<sup>33</sup> Resveratrol upregulates SIRT1 in human pulmonary alveolar epithelial cells, reduces ROS production, maintains the cell membrane potential, and inhibits apoptosis in alveolar epithelial cells, thus reducing hyperoxia-associated lung injury.<sup>34</sup> Resveratrol alleviates lung injury and apoptosis in paraquat-induced ALI in mice, via inhibition of NF- $\kappa$ B p65 translocation and cytokine production.<sup>35</sup> Protective effects of resveratrol were also shown in a rat model of chronic obstructive pulmonary disease (COPD) induced by cigarette smoke (CS) exposure combined with intratracheal injection of LPS, via reduction of endoplasmic reticulum stress-induced apoptosis in alveolar epithelial cells.<sup>36</sup> Moreover, resveratrol exhibits protective effects against CS extract-induced human bronchial epithelial cell apoptosis in vitro by preventing mitochondrial dysfunction and upregulating MFN2.<sup>37</sup> Vam3, a resveratrol dimer extracted from *Vitis amurensis* Rupr, also inhibits CS-induced apoptosis in the lung by improving mitochondrial function both in vitro and in vivo.<sup>38</sup> Resveratrol helps reduce sodium arsenite (NaAsO<sub>2</sub>)-induced oxidative and genetic damage as well as apoptosis by regulating glutathione homeostasis in human bronchial epithelial cells.<sup>39</sup> A previous study showed that resveratrol protects lung function by inhibiting apoptosis in rats with severe acute pancreatitis.<sup>40</sup> Another report demonstrated that resveratrol attenuates apoptosis in pulmonary microvascular endothelial cells induced by high shear stress with proinflammatory factors, by activating the SIRT1 signaling pathway and inhibiting oxidative-stress-dependent phenotypical shift in vitro.<sup>41</sup>

## Antioxidant effects

Oxidative stress is widely recognized to cause lung inflammation, which in turn leads to many lung diseases such as ALI, idiopathic fibrosis, pneumonia, asthma, and COPD.<sup>42</sup> Resveratrol was shown to exert protective effects against hyperoxic-lung injury via its anti-inflammatory and antioxidant properties in neonatal rats.<sup>43</sup> A protective effect of resveratrol was also shown in CS-induced lung oxidative injury in mice via decreased NF- $\kappa$ B activity and increased HO-1 expression and activity.<sup>44</sup> In vitro, resveratrol plays

a potential therapeutic role in lung epithelial cells infected with *Pseudomonas aeruginosa* by reducing ROS formation, ICAM-1 levels, human  $\beta$ -defensin-2 expression, and cell apoptosis markers, and upregulating glutathione peroxidase.<sup>45</sup> In addition, resveratrol attenuates *Streptococcus pneumoniae*-induced oxidative stress in lung epithelial cells.<sup>46</sup> Moreover, resveratrol significantly alleviates acute endotoxemia-associated lung injury via reduction of LPS-induced oxidative/nitrative stress in mice.<sup>47</sup> It is noteworthy that resveratrol attenuates LPS-induced EMT and pulmonary fibrosis in the murine model by suppressing oxidative stress and TGF- $\beta$ 1 signaling.<sup>48</sup> HMGB1 is one of the deteriorating factors involved in the development of ventilator-induced lung injury.<sup>49</sup> Resveratrol exerts protective effects against lung endothelial barrier dysfunction initiated by high tidal volume that involves inhibition of mechanical stretch-induced HMGB1 release and related oxidative damage of mitochondria, likely via an Nrf2-dependent mechanism in a mouse model of lung injury induced by mechanical ventilation.<sup>50</sup> Another report found that cospray dried resveratrol and budesonide inhalation formulation reduces inflammation and oxidative stress in LPS-induced rat alveolar macrophages.<sup>51</sup> In in vitro human model of oxidative damage response to arsenic trioxide (As<sub>2</sub>O<sub>3</sub>) exposure, resveratrol alleviates oxidative damage by maintaining glutathione homeostasis and inhibiting apoptosis in normal human lung cells.<sup>52</sup>

## Antifibrotic effects

Pulmonary fibrosis is characterized by continuous alveolar epithelial injury and dysregulated repair, which leads to fibroblast accumulation and excessive extracellular matrix deposition.<sup>53</sup> EMT causes epithelial cells to lose their apical basal polarity and cell–cell adhesion, and convert into mesenchymal cells, which play a potential role in lung fibrosis.<sup>54,55</sup> Bleomycin (BLM) is an antitumor drug that can cause pulmonary fibrosis during clinical treatment.<sup>56</sup> Repetitive intratracheal administration of BLM has been used to induce pulmonary fibrosis in animals for many years.<sup>57</sup> Meanwhile, resveratrol has shown antifibrotic effects in multiple tissues and organs, including the vessels, kidney, and liver in animal models.<sup>7,58,59</sup> As for the lung, resveratrol has protective effects in BLM-induced lung fibrosis in animals. Resveratrol alleviates the BLM-induced associated pathological changes, weight loss, and mortality in mice, and such effects may be associated with SIRT1 activation and the inhibition of EMT-associated molecular events in the mouse lung.<sup>60</sup> Similarly, polyphenols exhibit protective effects on the inflammatory process in mice with experimental pulmonary fibrosis.<sup>61</sup> In an

established rat model of BLM-induced lung fibrosis, resveratrol also exhibits some therapeutic potential.<sup>62</sup> A promising therapeutic potential for resveratrol was also demonstrated with decreased myofibroblast differentiation and extracellular matrix expression, and attenuated lung fibrosis in an established mouse model of BLM-associated lung fibrosis.<sup>63</sup> Furthermore, resveratrol exerts protective effects in paraquat-associated mitochondrial damage, oxidative stress, inflammation, and fibrotic reactions in normal human bronchial epithelial cells by activating the Nrf2 pathway.<sup>64</sup>

## Resveratrol reduces pulmonary hypertension

Pulmonary hypertension is a fatal disease characterized by sustained elevation of pulmonary vascular resistance and a progressive increase in pulmonary artery pressure accompanied by pulmonary vascular remodeling; this results in right ventricular hypertrophy, heart failure, and even death.<sup>65,66</sup> Monocrotaline (MCT) has been widely applied to induce pulmonary hypertension in animals.<sup>67</sup> Resveratrol was shown to exert protective effects in pulmonary hypertension both in vivo and in vitro. In vivo, resveratrol decreases MCT-induced pulmonary hypertension indices and normalizes the expression of pulmonary artery atrogin-1 mRNA, which is starkly decreased by MCT in rats.<sup>68</sup> In vitro, resveratrol significantly inhibits PDGF-induced cell proliferation and hypertrophy, which is also related to increased atrogin-1 levels in human pulmonary artery smooth muscle cells.<sup>68</sup> In addition, SIRT1 mediates the effects of resveratrol in regulating cell cycle regulatory molecules, contributing to pulmonary hypertension prevention, both in vitro and in vivo.<sup>69</sup> In a rat model of MCT-induced pulmonary hypertension, resveratrol exerts protective effects by preventing pulmonary arterial trunk remodeling, but not right ventricular hypertrophy.<sup>70</sup> Moreover, resveratrol inhibits MCT-induced right ventricular hypertrophy, which is mediated by the direct effects of resveratrol on cardiomyocytes as well as the indirect action of reducing pulmonary hypertension in rats.<sup>71</sup> A protective effect of resveratrol was also demonstrated in pulmonary thromboembolism-induced pulmonary hypertension via downregulation of MCP-1 and inhibition of acute pulmonary thromboembolism-induced p-p38 MAPK activation in rats.<sup>72</sup> Hypoxic pulmonary hypertension is characterized by progressive pulmonary artery constriction and remodeling. Pulmonary vascular remodeling, which is mainly caused by hypoxia-induced abnormal proliferation of human pulmonary artery smooth muscle cells, leads to sustained increase of pulmonary vascular resistance and hypoxic pulmonary

hypertension deterioration.<sup>73</sup> Resveratrol plays a beneficial role in reducing hypoxic pulmonary hypertension through anti-inflammatory and antioxidant pathways in rats.<sup>74</sup> Resveratrol was also shown to exert protective effects, by preventing human pulmonary artery smooth muscle cells arginase II induction and proliferation in hypoxic conditions through Akt-dependent signaling.<sup>75</sup> Moreover, a recent report showed that resveratrol exhibits protective effects by increasing right ventricular systolic pressure and reducing right ventricular hypertrophy in rats exposed to hypoxia alone, via increased SIRT1 activation.<sup>76</sup> Trimethoxystilbene (TMS, a resveratrol derivative), plays a beneficial role in the treatment of pulmonary hypertension both in vivo and in vitro. In vivo, TMS prevents hypoxia-induced pulmonary vascular remodeling and right ventricular hypertrophy, in association with inhibited NOX/VPO1 pathway as well as inflammatory reaction in rats.<sup>77</sup> In vitro, TMS inhibits proliferation and apoptosis in pulmonary artery smooth muscle cells stimulated with TNF- $\alpha$ .<sup>78</sup>

## Anticancer activities

Lung cancer is one of the most common malignant tumors that seriously endangers human life and health; it is classified as non-small-cell lung cancer (NSCLC, the most common type) and small-cell lung cancer. Despite the recent improvement in lung cancer treatment modalities, such as aggressive radio- and/or chemotherapy, less than 20% of patients survive for 5 years.<sup>79</sup> Low-dose resveratrol can inhibit lung cancer cell growth, via premature senescence induced by ROS-mediated DNA damage in NSCLC cells.<sup>80</sup> In addition, trans-resveratrol induces apoptosis via the mitochondrial-dependent pathway in human lung adenocarcinoma epithelial cells.<sup>81</sup> Furthermore, resveratrol was shown to exert protective effects in lung cancer cells via modulation of cell apoptosis and proliferation, by binding the synthetic or natural promoter of Egr-1, and upregulating GADD45 $\alpha$  in lung cancer A549 cells.<sup>82</sup> Resveratrol also effectively inhibits lung cancer growth by restraining the protumor activation of tumor-associated macrophages in human lung cancer.<sup>83</sup> Furthermore, resveratrol displays antitumor and antimetastatic effects by inhibiting lymphangiogenesis and regulating M2 macrophage activation and differentiation in tumor-associated macrophages.<sup>84</sup> Moreover, resveratrol inhibits proliferation and induces apoptosis by regulating p53, Bax, Bcl-2, and cleaved caspase-3 in lung adenocarcinoma cells, in a dose-dependent manner.<sup>85</sup> Resveratrol inhibits lung cancer in a dose-dependent manner both in vitro and in vivo.<sup>86</sup> In A549 cells, resveratrol exerts protective

effects against cancer mediated by STAT-3 signaling.<sup>87</sup> Furthermore, resveratrol inhibits hexokinase II mediated glycolysis by targeting the Akt signaling pathway in NSCLC to suppress tumor growth.<sup>88</sup> Multiple synthetic resveratrol analogs have been developed in recent years, including 3,4,4'-trihydroxy-trans-stilbene, which induces apoptosis and autophagy in NSCLC cells in vitro.<sup>89</sup> Studies have shown that resveratrol interacts with RNA to exert its antitumor effects. Interestingly, miR-200c sensitizes H460 cells to resveratrol, likely via RECK expression.<sup>90</sup> The novel long noncoding RNA AK001796 is involved in growth inhibition of lung cancer cells induced by resveratrol.<sup>91</sup> Meanwhile, resveratrol also shows protective effects against lung cancer by inducing considerable changes in the expression profile of microRNAs in A549 cells.<sup>92</sup> Moreover, resveratrol amplifies the effects of chemotherapy drugs in lung cancer. For example, resveratrol synergizes with gefitinib to increase intracellular concentrations of gefitinib and triggers apoptosis, autophagy, and senescence in gefitinib-resistant NSCLC cells.<sup>93</sup> In addition, resveratrol combination with cisplatin induces apoptosis by modulating autophagy in A549 cells.<sup>94</sup> Furthermore, resveratrol and arsenic trioxide synergistically induce apoptosis via ROS mediation of endoplasmic reticulum stress and mitochondrial dysfunction in A549 cells.<sup>95,96</sup> Moreover, resveratrol also interacts with other chemotherapeutic agents such as etoposide and erlotinib, to exert antitumor effects.<sup>79,97</sup>

## Limitations of resveratrol

In addition to protective effects on the respiratory system, resveratrol also protects against cardiovascular diseases, platelet aggregation, diabetes, and neurodegenerative diseases. The “French paradox” indicates that French individuals have lower incidence of cardiovascular diseases, which raises the question about the amount of wine one should drink to stay healthy. In vitro studies have shown that 111 glasses of wine should be consumed daily to achieve a baseline dose.<sup>98</sup> Despite the benefits of resveratrol in human health, its application in food and pharmaceutical industries is limited for a variety of reasons, including low bioavailability, water solubility, and chemical stability; indeed, this molecule is rapidly and extensively decomposed and excreted.<sup>99–101</sup> Indeed, the water solubility of resveratrol is too low without emulsifiers or stabilizers to produce the desired concentrations of aqueous solution.<sup>99</sup> Resveratrol is a highly light-sensitive compound, and exposure to light causes about 80%–90% of *trans*-resveratrol in solution to convert into *cis*-resveratrol.<sup>102</sup> Resveratrol is also easily degraded at high

temperature, as well as under pH change, ambient fluorescent light, or air exposure.<sup>101,103</sup> Two clinical trials have assessed the absorption and bioavailability of resveratrol, using a single 25 mg oral dose, which is equivalent to a moderate intake of red wine.<sup>100,104</sup> Despite the use of highly sensitive analytical methods and specific molecules, circulating plasma resveratrol was barely detectable. The low bioavailability of resveratrol is largely due to extensive metabolism in the gut and liver.<sup>105</sup> Meanwhile, in most studies, resveratrol is used in the free form, which is not suitable for drug delivery.<sup>106</sup> In recent years, various attempts have been made to improve the oral bioavailability of resveratrol, including complexation with  $\beta$ -cyclodextrins or hydroxypropyl- $\beta$ -cyclodextrins,<sup>107</sup> solid dispersion,<sup>108</sup> liposomes,<sup>109</sup> and lipid or polymeric nanoparticles.<sup>106,110</sup> Despite important advances, these technologies still face limitations, primarily with the use of large amounts of excipients and insufficient relevant bioavailability data. Therefore, new formulations may be a way to improve resveratrol's bioavailability and target specific organs.

## Conclusion

The protective effects of resveratrol in respiratory system diseases were discussed in terms of anti-inflammatory, anti-apoptotic, antioxidant, antifibrotic, antihypertensive, and antitumor properties, demonstrating a great potential for resveratrol in the treatment of respiratory system diseases. So far, only few clinical studies have analyzed the effects of resveratrol, including only a few patients. In addition, existing studies have focused on rodent models, with little efforts invested in animals closely related to humans, such as pigs and nonhuman primates. Therefore, future research should shift the focus to large animals and gradually transfer to clinical trials, while improving the stability and bioavailability of resveratrol. Such studies would provide a strong basis for the use of resveratrol, which has great therapeutic potential.

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## Disclosure

The authors report no conflict of interest in this work.

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