



Resveratrol for patients with chronic obstructive pulmonary disease: hype or hope?

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Purpose of review

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease with a high prevalence of extrapulmonary manifestations and, frequently, cardiovascular comorbidity. Resveratrol is a food-derived compound with anti-inflammatory, antioxidant, metabolic and cardioprotective potential. Therefore, resveratrol might improve the pulmonary as well as extrapulmonary pathology in COPD. In this review, we will evaluate knowledge on the effects of resveratrol on lung injury, muscle metabolism and cardiovascular risk profile and discuss if resveratrol is a hype or hope for patients with COPD.

Recent findings

Experimental models of COPD consistently show decreased inflammation and oxidative stress in the lungs after resveratrol treatment. These beneficial anti-inflammatory and antioxidant properties of resveratrol can indirectly also improve both skeletal and respiratory muscle impairment in COPD. Recent clinical studies in non-COPD populations show improved mitochondrial oxidative metabolism after resveratrol treatment, which could be beneficial for both lung and muscle impairment in COPD. Moreover, preclinical studies suggest cardioprotective effects of resveratrol but results of clinical studies are inconclusive.

Summary

Resveratrol might be an interesting therapeutic candidate to counteract lung and muscle impairments characteristic to COPD. However, there is no convincing evidence that resveratrol will significantly decrease the cardiovascular risk in patients with COPD.

Keywords

cardiovascular risk, chronic obstructive pulmonary disease, lung pathology, muscle mitochondrial function, resveratrol

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease characterized by persistent airflow obstruction and lung inflammation primarily caused by inhalation of cigarette smoke [1]. The pulmonary inflammation involves macrophages, epithelial cells, dendritic cells, neutrophils, eosinophils and T and B-lymphocytes which release many inflammatory mediators that contribute to the pathophysiology of COPD [2]. Furthermore, antioxidant capacity is reduced in COPD, whereas oxidant release from increased activated inflammatory cells is increased [2]. The resulting oxidative stress is even further increased during exacerbations and may be associated with increased inflammation, airway remodeling and corticosteroid resistance [3].

Next to the respiratory impairment, extrapulmonary manifestations and comorbidities contribute to disease burden and mortality [1]. Cardiovascular disease is a common comorbidity in patients with COPD and is even the leading cause of mortality in patients with mild-to-moderate COPD [4]. Furthermore, skeletal muscle wasting is highly prevalent in

COPD, in particular in patients with emphysema [5], and is associated with intrinsic muscular abnormalities [6]. A shift from less oxidative type-I toward more glycolytic type-II muscle fibers has been consistently reported in lower limb muscles of patients with COPD [7] and markedly decreased phosphorylated adenosine monophosphate-activated protein kinase (AMPK) and peroxisome proliferator-activated

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KEY POINTS

- Resveratrol targets both lung and muscle via overlapping mechanisms involved in lung and muscle impairment in COPD.
- From a lung and skeletal muscle perspective in COPD there is hope for resveratrol.
- Clinical evidence for resveratrol as adjunct to or alternative for proven lifestyle interventions to decrease the cardiovascular risk is inconclusive due to heterogeneity in dosage and duration of resveratrol supplementation.
- Human clinical studies investigating the effect of resveratrol on lung damage and/or skeletal muscle mass or mitochondrial dysfunction should be performed.

receptor gamma coactivator 1-alpha (PGC-1 α) protein levels were observed in muscle biopsies of COPD patients [8–10]. In addition, these patients rely more on the metabolically less-efficient complex-II driven mitochondrial respiration [11[■]]. Moreover, increased reactive oxygen species production has been observed in skeletal muscle mitochondria of patients with COPD compared with controls [12]. The respiratory muscles are also affected in patients with COPD, mainly due to lung hyperinflation and increased airway resistance and obstruction but also by systemic factors such as inflammation and oxidative stress [13]. In contrast to lower limb muscle, the diaphragm has an increased proportion of type-I fibers and increased mitochondrial and capillary content [13]. Boosting muscle oxidative metabolism could be beneficial for patients with COPD by stimulating adaptive changes in respiratory muscles and/or reversing altered cellular energy metabolism in limb muscle.

The natural polyphenol resveratrol (3,5,4'-trihydroxystilbene) might be an interesting therapeutic candidate for COPD by simultaneously targeting both pulmonary as well as extrapulmonary pathology. Interest in resveratrol started when cardioprotective effects of red wine were identified [14]. Nowadays, resveratrol is receiving increasing interest because of its potential to improve metabolic health and its anti-inflammatory and antioxidant properties [15[■],16,17], which might also benefit the lungs and muscles. Beneficial effects of resveratrol have been reviewed in relation to aging, obesity or diabetes [15[■],18,19], but not in relation to COPD. Here we will therefore evaluate available evidence regarding the effects of resveratrol on lung injury, muscle metabolism and cardiovascular risk profile and discuss if resveratrol supplementation is just a hype or could give hope to patients with COPD.

THE MECHANISMS OF ACTION OF RESVERATROL

Resveratrol exerts its beneficial health effects through several signaling pathways which have been reviewed elsewhere [15[■],18,20–22]. Here we will briefly summarize the processes and molecular pathways affected by resveratrol and relevant for COPD, focusing on molecular targets to decrease lung and muscle impairment. The most relevant target for the downstream effects of resveratrol is Sirtuin 1 (SIRT1), a nicotinamide adenine dinucleotide-dependent histone deacetylase that promotes cell survival, which is activated by resveratrol directly or indirectly via the activation of AMPK [15[■]]. Activation of SIRT1 has been proposed to be involved in a number of beneficial health effects of resveratrol. First of all, SIRT1 activates PGC-1 α , a master regulator of mitochondrial metabolism and biogenesis [15[■]]. This beneficial effect of resveratrol may improve mitochondrial function which is known to be compromised in muscles and lungs of patients with COPD [10,23[■]]. Second, SIRT1 activation can modulate several stress response transcription factors such as forkhead box O (FOXO)3 which regulates autophagy [18,21]. Autophagy is the process of eliminating organelles and proteins through the lysosomal degradation pathway; it is increased in both lungs and skeletal muscle of patients with COPD [24,25]. Third, SIRT1 downregulates the transcription factor nuclear factor kappa B (NF- κ B) which is involved in the anti-inflammatory properties of resveratrol [22]. Activation of SIRT1 inhibits degradation of the inhibitor of κ B, inhibiting the translocation of NF- κ B to the nucleus and reducing the expression of inflammatory and immune genes including proinflammatory cytokines, chemokines, inflammatory enzymes and adhesion molecules [22]. Other putative pathways responsible for the anti-inflammatory properties of resveratrol have been described elsewhere [22], but as most inflammatory proteins upregulated in COPD macrophages are regulated by NF- κ B pathway [24], this pathway would be most interesting for resveratrol in COPD.

In addition, resveratrol exerts its antioxidant effects mainly through regulation of nuclear factor erythroid-2-related factor-2 (Nrf2). By inhibiting proinflammatory cytokines and oxidative stress Nrf2 plays a protective role against inflammation in cells [20]. Normally Nrf2 is activated by oxidative stress; however, in COPD, activation is not appropriate despite high levels of oxidative stress in the lungs [24]. Activation of Nrf2 leads to the induction of many antioxidant enzymes including heme-oxygenase-1, superoxide dismutase, glutathione peroxidase, and

catalase and can be protective against damage, inflammation and oxidative cell death [18]. The activation of Nrf2 is also suggested to be mediated by SIRT1 [26]. The described anti-inflammatory and antioxidant properties of resveratrol can also contribute to cardiovascular protective effects as reviewed elsewhere [27[■]].

EFFECTS OF RESVERATROL ON LUNG DAMAGE

Anti-inflammatory and antioxidant properties of resveratrol in the lungs have been demonstrated in preclinical models. Resveratrol causes a reduction in lung tissue neutrophilia and proinflammatory cytokines in a rodent model of acute lipopolysaccharide (LPS)-induced airway inflammation [28]. Furthermore, *in-vitro* treatment with resveratrol inhibited the release of inflammatory cytokines from bronchoalveolar lavage fluid macrophages and human bronchial smooth muscle cells isolated from COPD patients [29–32]. These anti-inflammatory effects of resveratrol were ascribed to the inhibition of NF- κ B activation [32]. Resveratrol has also been shown to inhibit autophagy *in vitro* in human bronchial epithelial cells and *in vivo* in a LPS and cigarette smoke-induced COPD mice model by reversing the decrease in SIRT1 and FoxO3a expression and by decreasing the production of Beclin1 protein [33[■],34,35].

Long-term cigarette smoke exposure caused persistent oxidative stress-induced impairments in mitochondrial structure and function in human bronchial epithelial cells [36]. This mitochondrial dysfunction is also involved in the pathogenesis of COPD and may be related to a reduction in PGC-1 α [23[■]]. Resveratrol has been shown to attenuate cigarette smoke-induced oxidative stress in human lung epithelial cells via nuclear translocation of Nrf2 [37,38], possibly mediated by SIRT1 [38]. Moreover, intratracheal instillation of resveratrol in mice caused increased SIRT1 levels and maintained PGC-1 α in alveolar epithelial cells [39[■]]. These mitochondrial effects were correlated with maintenance of lung structure and function.

Corticosteroids are able to suppress the release of inflammatory mediators in macrophages, but fail to sufficiently suppress airway inflammation in stable COPD [40]. Furthermore, long-term treatments with oral corticosteroids bear high risks of significant adverse effects such as increasing blood glucose levels, muscle atrophy and abdominal obesity [41]. Resveratrol could be an alternative treatment for corticosteroids in COPD. Indeed, in cultured human airway, smooth muscle cells exposed to TNF- α resveratrol reduced the release of inflammatory mediators more efficiently than dexamethasone [31]. Furthermore,

resveratrol was superior to dexamethasone in reducing COPD-associated cytokines and matrix-metalloproteinase-9 in human airway smooth muscle cells and alveolar macrophages [30,42]. These potential effects of resveratrol have led to the development of a spray-dried resveratrol powder [43,44[■]], which showed anti-inflammatory activities *in vitro* [44[■]].

The various reported experimental models consistently show beneficial effects of resveratrol on inflammatory processes and oxidative stress markers in the lungs. However, up till now no clinical proof-of-concept studies are available to confirm these results in a clinical setting.

EFFECTS OF RESVERATROL ON SKELETAL MUSCLE MASS AND MITOCHONDRIAL HEALTH

The described mechanisms of action suggest that resveratrol can both improve skeletal muscle oxidative metabolism and maintain skeletal muscle mass. Timmers *et al.* [45] were the first to confirm improved mitochondrial metabolism in a clinical proof-of-concept study, as increased muscle protein expression of AMPK, SIRT1, PGC-1 α and citrate synthase were observed after 30 days of 150 mg/day resveratrol supplementation in healthy obese men. Although another study including 10 patients with type 2 diabetes mellitus (T2DM) also found increased SIRT1 after 12 weeks of resveratrol (3 g/day) [46], three other studies including T2DM, obese and nonobese patients did not find increased mitochondrial biogenesis markers after resveratrol treatment, despite comparable dosage and duration [45,47,48]. In addition, improved muscle mitochondrial respiration on the electron input of both complexes I and II and increased maximal capacity of the electron transport chain was found after resveratrol supplementation in overweight and obese patients [45,49[■]] and in T2DM patients [50[■]]. In these studies, no differences in mitochondrial content were found, suggesting that mitochondria became more efficient. Contradictory, another study found an increased mitochondrial number after 6 weeks of resveratrol in older adults, despite no changes in mitochondrial size and morphology [51[■]]. However, a higher dose of resveratrol (2–3 g/day) was used compared with the studies that did find an improvement in mitochondrial respiration (80–150 mg/day) [45,49[■],50[■]]. In addition, an increment in the oxidative type-I myosin heavy chain protein in primate soleus muscle was found after long-term resveratrol treatment [52[■]]. To our knowledge, only one study investigated the effect of resveratrol on skeletal muscle mRNA and protein expression levels in a model of COPD [53]. In rats exposed to cigarette

smoke and LPS, supplementation with resveratrol lowered serum and muscle TNF- α accompanied by an increase in AMPK. Altogether, these results show promising results of resveratrol on skeletal muscle oxidative metabolism.

Preliminary data also suggest several beneficial effects of resveratrol on skeletal muscle mass maintenance. In C2C12 myotubes and in mice, muscle atrophy, induced by TNF- α or glucocorticoids, was inhibited by resveratrol through inhibition of the atrogenes downstream of the Akt/mTOR/FOXO1 signaling pathway [54–56]. In addition, resveratrol reduced the expression of palmitate-induced inflammation in C2C12 myoblasts by mechanisms involving the inhibition of oxidative stress and decreasing the activity of NF- κ B [57[■]]. Moreover, loss of oxidative capacity is postulated to accelerate the process of muscle loss [58]. Therefore, improving the skeletal muscle oxidative capacity might maintain skeletal muscle mass. These preclinical effects of resveratrol on skeletal muscle maintenance have not been observed in human clinical studies yet [48,49[■],59[■]], possibly because the studied populations (i.e. healthy obese or nonobese individuals with metabolic syndrome) were not characterized with muscle wasting.

EFFECTS OF RESVERATROL ON THE CARDIOVASCULAR RISK PROFILE

Preclinical animal studies have suggested beneficial effects of resveratrol for the treatment of

cardiovascular diseases as was recently reviewed [27[■],60,61]. However, these reviews also revealed that clinical studies produced inconsistent results and were not as promising as preclinical data. Nevertheless, a recent meta-analysis including overweight and obese participants showed that SBP, fasting glucose and total cholesterol were significantly lower after resveratrol supplementation, whereas other cardiovascular risk parameters remained unaltered [62[■]]. More specifically, a subgroup analysis showed that beneficial effects of resveratrol were found at a high dose of resveratrol (≥ 300 mg/day). The variability in dosage (8–3000 mg/day) and duration (2 weeks to 6 months) between studies and the low bioavailability of resveratrol [63] can contribute to the variation in results between studies. The fact that some cardiovascular risk parameters were lowered in a group of individuals at risk for cardiovascular disease still implicates that there is potential for resveratrol to decrease the cardiovascular risk. In COPD, not only obese patients but even normal weight patients are already at an increased cardiovascular risk [64[■],65].

RESVERATROL IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Resveratrol could be an interesting intervention for COPD as it targets both lung and muscle via overlapping mechanisms (Fig. 1). First of all, the anti-inflammatory properties of resveratrol can reduce both lung and muscle impairment and may

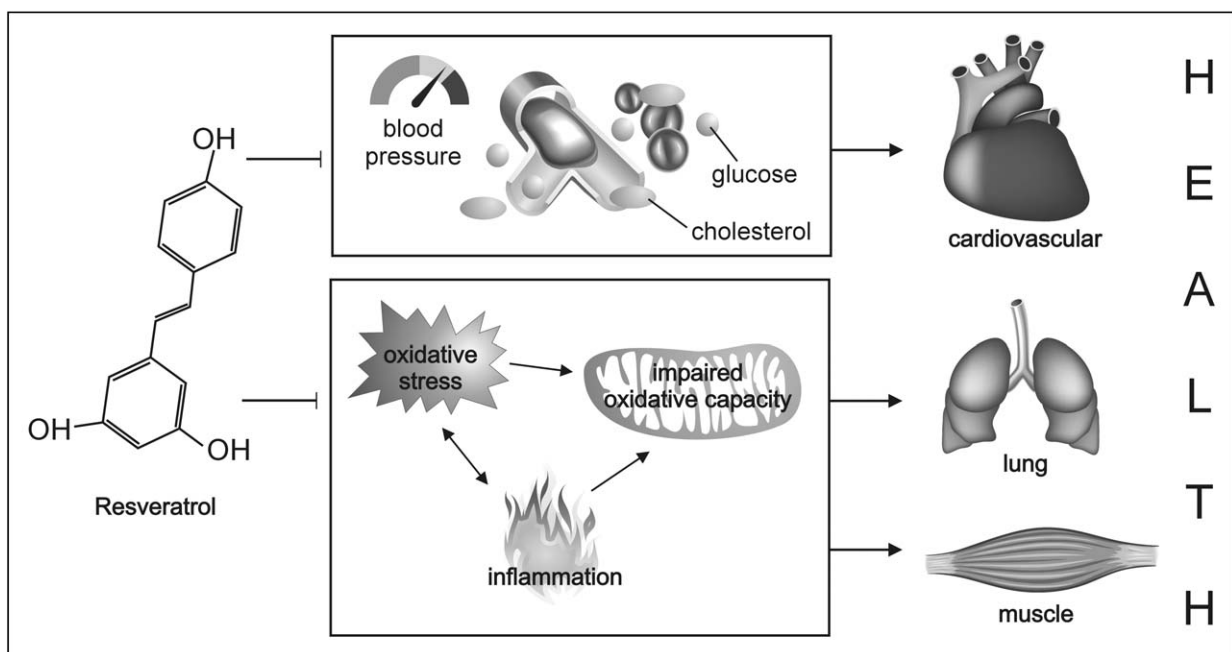


FIGURE 1. Schematic overview of the beneficial effects of resveratrol on lung impairment, muscle metabolism and cardiovascular disease risk in patients with chronic obstructive pulmonary disease.

potentially even reduce the need for anti-inflammatory drugs with their negative side-effects. Systemic inflammation, measured by NF- κ B, TNF- α and matrix-metalloprotease-9 protein expression in lymphocytes, was increased in COPD patients compared with healthy controls and was reduced after resveratrol treatment [66[■]]. This increased systemic inflammation may affect both the lungs and muscles [24]. Moreover, increased macrophage numbers in the lungs play a key role in the pathophysiology of COPD and most inflammatory proteins upregulated in these macrophages are regulated by NF- κ B [24]. Inflammatory modulation in the lungs would therefore be beneficial for COPD. As systemic inflammation has been implicated in skeletal muscle wasting, loss of lower limb mitochondrial capacity and deterioration of respiratory muscles [13,67], the anti-inflammatory effects of resveratrol would also benefit the muscular impairments in COPD.

Resveratrol not only improves mitochondrial oxidative capacity indirectly via its anti-inflammatory properties, but also directly via the AMPK-SIRT1-PGC-1 α axis. Again this beneficial effect of resveratrol can affect both the muscle and the lung as SIRT1 levels and PGC-1 α are decreased in both lung and muscle tissue of patients with COPD [9,10,23[■],68]. Preclinical findings suggest that inhaled resveratrol can improve mitochondrial function in the lungs and subsequently maintain lung structure and function in COPD [39[■]]. In muscle, nutritional supplementation with resveratrol showed improved mitochondrial function accompanied by improved mitochondrial respiration in obese men [45].

Finally, the antioxidant properties of resveratrol may affect both the lungs and the skeletal muscle as well. In COPD patients, high levels of oxidative stress have been observed in the lungs and have been associated with increased inflammation, airway remodeling, autoimmunity and corticosteroid resistance [3]. Reducing oxidative stress would therefore be beneficial to decrease lung injury in COPD. Moreover, many studies indicate an important role of oxidative stress, in skeletal and respiratory muscle dysfunction and loss of skeletal muscle mass in patients with COPD [6,13,69].

Because of the overlapping mechanisms in lungs and skeletal muscle that can be improved by resveratrol, treatment with resveratrol would be even more interesting for specific phenotypes of patients with COPD. For example, the cachectic COPD phenotype, characterized by high prevalence of emphysema and muscle wasting [5], display more severe abnormalities in muscle oxidative phenotype which could be improved by resveratrol [58]. Furthermore, patients with COPD who often experience exacerbations

would be another interesting population for resveratrol treatment, as exacerbations are often accompanied by pulmonary and systemic inflammation and are associated with increased susceptibility to muscle wasting [70].

On top of the beneficial effects of resveratrol on the lungs and muscle, preclinical studies suggest cardioprotective effects of resveratrol. Cardiovascular risk modification is currently underappreciated in COPD management and should receive more attention. Early assessment of the cardiovascular risk profile is expected to result in the initiation of risk-lowering therapies. Despite overwhelming attention to resveratrol in the cardiovascular risk context, we conclude that clinical evidence for resveratrol is inconclusive due to the large variability in dosage and duration. Therefore, it is still unclear whether resveratrol can be used as adjunct or alternative for proven lifestyle interventions including smoking cessation, physical activity and nutritional and dietary modulation, to improve the cardiovascular risk in COPD.

CONCLUSION

Resveratrol seems a promising candidate to decrease lung injury and to improve skeletal muscle mitochondrial function which is known to be compromised in COPD. However, there is no convincing evidence that resveratrol will significantly decrease the cardiovascular risk in patients with COPD.

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Conflicts of interest

There are no conflicts of interest.

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