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*Review: Current Opinion in Pharmacology*

**Targeting oxidant-dependent mechanisms for the treatment of  
respiratory diseases and their comorbidities**

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## **Abstract**

Oxidative stress is implicated in the pathogenesis of respiratory diseases, such as COPD and its comorbidities, asthma, idiopathic pulmonary fibrosis and radiation pneumonitis. Antioxidants drugs, such as small molecule thiols, nuclear erythroid-2 related factor 2 activators and catalytic enzyme mimetics have been developed to target oxidant-dependent mechanisms. The therapeutic effects of antioxidants have been generally disappointing. A small number of antioxidants are approved for clinical use, such as the small molecule thiol N-acetyl-L-cysteine for chronic obstructive pulmonary disease, and in the United States, the superoxide dismutase mimetic AEOL 10150 for severe radiation pneumonitis. The future use of antioxidants for the treatment of chronic respiratory diseases may require a precision medicine approach to identify responsive patients.

**Word count:** 115 words

## **Key words**

Oxidative stress; antioxidants; respiratory disease; COPD; asthma; idiopathic pulmonary fibrosis; radiation pneumonitis; small molecule thiols; Nrf2 activators; catalytic antioxidant enzyme mimetics

Chemical compounds studied in this article N-acetyl-L-cysteine (PubChem CID: 12035); Carbocisteine (PubChem CID: 193653); Erdosteine (PubChem CID: 65632); Dimethyl fumarate (PubChem CID: 637568); Bardoxolone methyl CDDO (PubChem CID: 400769); AEOL-10150 (PubChem CID: 24978527); Ebselen (PubChem CID: 3194); BXT-51072 (PubChem CID: 130165); Edaravane (PubChem CID: 4021); Apocynin (PubChem CID: 2214).

## Introduction

Oxidant-antioxidant (redox) balance in the respiratory system is an important component of host defense against pathogens. Oxidative stress occurs when oxidants overwhelm neutralizing antioxidants due to excess generation of free radicals, termed reactive oxygen species (ROS) and reactive nitrogen species (RNS) and/or due to reduced endogenous antioxidant defences [Figure 1]. The generation of ROS occurs from exposure to exogenous factors, such as cigarette smoke, atmospheric pollutants and ionizing radiation and from endogenous sources including inflammatory cells, such as activated macrophages and neutrophils, epithelial cells and by the activation of intracellular oxidative enzymes, such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX2). ROS contains one or more unpaired electrons, a state that makes them highly reactive and unstable. Important ROS that contribute to oxidative stress are oxygen radicals, such as the superoxide anion ( $O_2^{\bullet-}$ ) and hydroxyl radical ( $HO^{\bullet}$ ) and nonradical species, such as hydrogen peroxide ( $H_2O_2$ ). RNS include nitric oxide ( $^{\bullet}NO$ ), peroxynitrite ( $ONOO^-$ ) and nitrogen dioxide ( $^{\bullet}NO_2$ ). Antioxidant defenses against ROS occurs by the activation of the endogenous enzymes superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) and by non-enzymatic antioxidants that include albumin, mucin and dietary sources, such as vitamins E (tocopherol), vitamin C (ascorbic acid), carotenoids and flavonoids.

Excess oxidative stress causes DNA damage, protein carbonylation and lipid peroxidation and these adverse effects are thought to contribute to lung injury in respiratory diseases. Increased oxidative stress is implicated in the pathogenesis of chronic obstructive pulmonary disease

COPD [1-4] and its associated co-morbidities including cardiovascular diseases [2], osteoporosis [5] and skeletal muscle wasting [2,6] and in the pathogenesis of asthma [7,8], cystic fibrosis [9,10], bronchiectasis [11], idiopathic pulmonary fibrosis (IPF) [12,13], pulmonary hypertension [14] and radiation pneumonitis [15]. Detailed reviews on the pathways involved in oxidant-antioxidant balance in chronic respiratory diseases are published elsewhere [1,3,4,16,17].

Targeting oxidant-dependent mechanisms is a potentially attractive approach to the treatment of chronic respiratory diseases and their comorbidities. This review summarizes the results of recent clinical trials of antioxidants in several chronic diseases, discusses their place in management and considers the reasons for the failure of many synthetic antioxidants to reach the clinic.

## **Interventions to target oxidative stress**

Small molecule synthetic drugs and dietary supplements have potential antioxidant properties that suggest that they may be effective in the treatment of respiratory diseases (Table 1).

However, only a few of these compounds have been evaluated in large clinical trials.

### **Small molecule thiol antioxidants**

Small molecule thiol drugs decrease oxidant activity by increasing the synthesis of intracellular glutathione levels in depleted cells, although their antioxidant effect is considered to be weak when glutathione levels are normal [18]. Thiol drugs also reduce disulfide bonds in mucus

glycoproteins to produce mucolytic effects. In the treatment of respiratory diseases that are associated with chronic mucus hypersecretion, it is uncertain whether the clinical benefits of small molecule thiol drugs are due to their antioxidant and/or mucolytic properties.

N-acetyl-L-cysteine (NAC) is the most frequently investigated small molecule thiol antioxidant for the treatment of chronic respiratory diseases, mainly COPD and IPF. Several large randomized controlled clinical trials have investigated the clinical benefits of treatment with NAC in patients with COPD [19,20]. In the BRONCUS (Bronchitis Randomized on NAC) study, 523 patients with COPD received 600 mg daily NAC or placebo for 3 years. NAC had no effect on the primary outcomes of yearly decline in FEV<sub>1</sub> and number of exacerbations per year [19]. More recently, the PANTHEON (Placebo-controlled study on efficacy and safety of N-acetylcysteine High dose in Exacerbations of chronic Obstructive pulmonary disease) study investigated the clinical effects of higher dose NAC (600 mg twice daily) in 1006 Chinese patients with moderate to severe COPD [20]. Higher dose NAC reduced the rate of exacerbations, that were mainly mild in severity, by 22% compared with placebo over one year. A further small trial of high dose NAC treatment reported reductions in exacerbation rates in Chinese patients with COPD [21] who were at a high risk of an exacerbation [22]. A meta-analysis of 13 studies in 4155 patients with COPD that were treated with low dose (<600 mg daily) or high doses of NAC concluded that the lower dose was effective in reducing exacerbations of chronic bronchitis, whereas the higher dose was required to prevent exacerbations in patients with spirometric evidence of COPD [23]. The beneficial effects and safety of oral and inhaled NAC treatment has been investigated in several recent clinical trials in IPF [24-26]. The PANTHER-IPF trial (Prednisone, Azathioprine, and

N-Acetylcysteine: A Study That Evaluates Response in Idiopathic Pulmonary Fibrosis) reported that oral NAC compared to placebo resulted in no difference in the rate of decline in forced ventilatory capacity (FVC), death rate or acute exacerbations in patients with IPF with mild to-moderate impairment in lung function over a 60-week period [26]. The PANAMA trial assessed the safety and tolerability of oral NAC or placebo for 24 weeks in 123 patients with IPF with background treatment of pirfenidone and reported that although NAC was well tolerated, its use may have increased the rate of decline in FVC [27].

Carbocisteine and erdosteine are thiol antioxidant and mucolytic drugs that have been investigated as long-term treatments for COPD. The PEACE study reported that 1500 mg carbocisteine daily decreased exacerbations rates over 1 year in Chinese patients with COPD [28]. A systematic review and meta-analysis of 4 studies involving 1357 patients, including participants in the PEACE trial, concluded that long-term treatment with carbocisteine reduced exacerbation rates and improved the quality of life of patients with COPD [29]. The RESTORE (Reducing Exacerbations and Symptoms by Treatment with ORal Erdosteine in COPD) study in 445 patients with stable moderate-to-severe COPD (GOLD stage 2 and 3) reported that the addition of erdosteine 600 mg daily to usual therapy compared to placebo over a 1 year decreased the rate of mild exacerbations, but not the rate of moderate and severe exacerbations and reduced the duration of exacerbations, irrespective of severity [30]. A meta-analysis of older studies investigating the treatment effects of erdosteine 600 mg daily compared with placebo in patients with COPD and/or chronic bronchitis, of whom



approximately half were treated during an exacerbation, reported reductions in self-reported acute respiratory symptoms [31].

A pair-wise and network meta-analysis of 11 trials of mucolytic/antioxidant agents including NAC (n=6), carbocysteine (n=3) and erdosteine (n=1) on COPD exacerbations demonstrated that they prevented exacerbations as maintenance add-on therapy to patients with frequent exacerbations (11 studies analyzed, odds ratio (OR) 0.51, 95% confidence interval (CI) 0.39–0.67;  $p < 0.001$ ) [32]. The most effective drug was NAC 1,200 mg daily, whereas NAC 600 mg daily was no more effective than placebo. The effectiveness of mucolytic/antioxidant agents was independent of the severity of airway obstruction and the use of inhaled corticosteroids. A Cochrane systematic review found no evidence of clinical benefit from nebulized or oral thiol derivatives in the treatment of cystic fibrosis [33].

The 2017 GOLD (Global Initiative for Chronic Obstructive Lung Disease) guideline considers that the evidence is sufficient to indicate that NAC and carbocysteine reduce exacerbations and modestly improve quality of life in selected patients (Evidence A). The guideline does not provide recommendations about which patients, GOLD groups A to D, these drugs should be used [34]. The American Thoracic Society/European Respiratory Society clinical practice guideline on the treatment of IPF has a conditional recommendation against the use of inhaled or oral NAC monotherapy [24]. The US Cystic Fibrosis (CF) Foundation Pulmonary Clinical Practice Guidelines Committee Guideline concludes that in individuals with CF aged 6 years and older the evidence is insufficient to recommend for or against the chronic use of inhaled or oral NAC to improve lung function and quality of life or reduce exacerbations [35].

### **Nuclear erythroid-2 related factor 2 activators**

Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is an important transcript factor of antioxidant defense [36]. The Nrf2 activating molecule sulforaphane improves phagocytosis of bacteria in alveolar macrophages of patients with COPD [37]. A 4 week clinical trial of sulforaphane did not increase Nrf2 target gene expression, decrease markers of oxidative stress or improve lung function in patients with COPD [38]. The Nrf2 activator dimethyl fumarate (BG-12), which is approved in the US for the treatment of multiple sclerosis [39] is undergoing investigation in an inhaled microparticulate powder formulation for the treatment of respiratory disorders [40], but currently no clinical studies are underway in COPD or IPF [41]. Several synthetic CDDO (2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid) Nrf2 activators have been developed for clinical use [42] and of these, bardoxolone methyl CDDO is being assessed in pulmonary hypertension [41].

### **Catalytic antioxidant enzyme mimetics**

Catalytic antioxidant enzyme mimetics attenuate oxidative stress by restoring the action of depleted intracellular antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) [43]. There are 3 human isoforms of SOD, each of which can transform  $O_2^{\bullet-}$  to  $H_2O_2$ . SOD mimetics include metalloporphyrins, such as and AEOL-10150, macrocyclic ligands, such as M40419, and salens, such as EUK-134 or EUK-189 [17]. The U.S. Food and Drug Administration (FDA) recently granted fast track designation to AEOL 10150 for

the treatment of severe radiation pneumonitis following exposure to acute high dose radiation. GPx-1 is proposed as a potential therapeutic target for the treatment of COPD [44]. GPx mimetics include ebselen, a selenium-based organic compound and BXT-51072, although currently, neither compound is registered as undergoing clinical trial evaluation in respiratory diseases [41].

### **Other synthetic small molecule antioxidants**

In addition to the antioxidants drugs reviewed above, other synthetic small molecules have been developed as potential antioxidant treatments for oxidative stress in human diseases, including chronic respiratory diseases (Table 1). Currently, none of these compounds are registered as undergoing clinical trial evaluation in respiratory diseases [41]. Lipid peroxidation inhibitors, such as edaravane (MC-186), which is approved for the treatment of amyotrophic lateral sclerosis and the lazaroid antioxidant molecule, U-83836E, have been developed for clinical use. Inhaled glutathione does not improve clinical outcomes and markers of oxidative stress in cystic fibrosis [45], asthma [46] or IPF [47]. Spin traps are free radical scavengers and a phenyl-based nitron spin trap derivative, disufenton sodium (NXY-059) was investigated as a neuroprotective agent, but it failed in clinical trials [48]. Thioredoxin mimetic peptides (redox sensors) attenuate oxidative stress and these compounds are undergoing pre-clinical development for the treatment of radiation-induced fibrosis and IPF [49]. Nebulized apocynin preferentially blocks NOX-2 and reduces reactive oxygen species concentrations in exhaled breath condensate in patients with mild asthma [50] and in COPD [51]. Neutrophilic-induced

tissue damage is in part induced by myeloperoxidase (MPO)-derived oxidants. Inhibitors of MPO have been developed [52], such as AZD3241 and INV-315. The MPO inhibitor AZ1 inhibits the progression of emphysema and small airway remodeling in a smoke-induced animal model of COPD [53]. Selective inhibitors of inducible nitric oxide synthase (iNOS), such as GW274150 attenuates inflammation in experimental models of COPD [54].

### **Naturally occurring dietary antioxidant supplements**

A wide range of naturally occurring dietary products have antioxidant properties (Table 1). Polyphenols are water-soluble molecules found in fruits, vegetables, red wine, tea and in a Mediterranean diet and include compounds such as resveratrol, green tea catechins and curcumin. Other dietary antioxidants include vitamins C and E, carotenoids, such as  $\beta$ -carotene, minerals including zinc and selenium and various nutritional supplements. A small number of trials have examined the effectiveness of antioxidant supplements on the treatment or prevention of chronic respiratory diseases or comorbidities associated with COPD. Most studies have shown no beneficial effects. Dietary antioxidants or vitamin supplements are not effective in reducing the risk of developing comorbidities that are often associated with COPD, such as cardiovascular disease [55] and cancer [55] or are of limited benefit in improving skeletal muscle dysfunction in COPD in comparison to exercise training alone [56]. Antioxidants may be of benefit in treating osteoporosis associated with COPD [2,5]. A systematic review of vitamin E supplementation reported no clinical benefits in patients with cystic fibrosis [57]. Some trials report improvements in clinical outcomes with antioxidant supplements in respiratory diseases.

For example, a large randomized trial of vitamin E supplements led to a 10% reduction in the risk of chronic lung disease (asthma, emphysema, chronic bronchitis, bronchiectasis) in women [58]. Some small clinical trials report that dietary antioxidants or vitamin supplements improve asthma control or lung function in children or adults with asthma [59,60], whereas a trial of broccoli sprouts, which is a rich source of sulforaphane was ineffective in improving biomarkers of airway inflammation or clinical outcomes in adults with atopic asthma [61]. Several clinical trials of dietary supplements are underway for the treatment of chronic respiratory diseases, including one investigating the effects resveratrol in modulating metabolism and cardiovascular risk profile in patients with COPD [41].

## **Conclusions**

There is convincing evidence that oxidative stress is involved in the pathogenesis of respiratory diseases, such as COPD and its comorbidities, asthma, bronchiectasis, cystic fibrosis, idiopathic pulmonary fibrosis, pulmonary hypertension and radiation pneumonitis. Targeting oxidant-dependent mechanisms should be a promising therapeutic approach to the management of chronic respiratory disease. Although many synthetic drugs and naturally occurring dietary substances have antioxidant properties, only a relatively small proportion of these agents have undergone clinical trial evaluation in respiratory diseases. Overall, the therapeutic effects of antioxidants in different respiratory diseases has been generally disappointing. Treatment with small molecule thiol compounds, particularly NAC, have shown improvement in clinical outcomes including mild exacerbations in COPD, whereas their effectiveness in preventing

severe exacerbation in patients receiving maximal usual therapy is less certain. The FDA recently granted fast track designation to the SOD mimetic AEOL 10150 for the treatment of severe radiation pneumonitis following exposure to acute high dose radiation. Other synthetic antioxidant drugs have not been approved for clinical use in the treatment for chronic respiratory diseases.

Several reasons may explain the failure of many synthetic antioxidants to reach the clinic. Clinical pharmacological factors, such as inadequate dose or inappropriate route of administration or formulation of the antioxidant are likely to be important in some trials. In other trials, there are limitations in study design, such as small sample size. Patient-related characteristics, such as genetic susceptibility, age, race, history of chronic bronchitis or exacerbations, baseline levels of redox balance, diet, and concurrent medications may also modify the response to antioxidants. The underlying concept that oxidative stress can be defined by an imbalance between pro-oxidants and antioxidants may be an oversimplification of redox signalling systems and in the absence of antioxidant deficiency, antioxidants may be ineffective in reversing oxidative stress related tissue damage [13,62].

The use of antioxidants in the treatment of chronic respiratory diseases in the future may require the use of precision medicine to identify patients that are likely to benefit from these therapeutic interventions. For example, clinical trials are required to assess the benefits of small molecule thiol compounds in people with chronic bronchitis associated with COPD or asthma, including asthmatic smokers [63]. Biomarkers may help establish antioxidant deficiency

or a high burden of oxidative stress prior to treatment with antioxidant drugs. Genotypes of responsiveness to NAC, such as the gene encoding toll-interacting protein (TOLLIP) TT genotype [64] may identify subgroups of patients with IPF for treatment [64]. The recognition that oxidative stress is associated with inflammation suggests that future trials should investigate the therapeutic effects of the administration of antioxidants in combination with anti-inflammatory therapies [65] or the combination of antioxidant drugs with different modes of action. Finally, the finding that a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events in people at a high cardiovascular risk [66] should prompt future trials of this diet in the management of chronic respiratory diseases and their comorbidities.

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### **Declaration of interest**

Conflicts of interest: none.

**Table 1 Potential synthetic antioxidant drugs and naturally occurring dietary antioxidant supplements**

Category of antioxidant	Examples
<b>Small molecule thiol antioxidants</b>	N-acetyl-L-cysteine [NAC] Carbocisteine Erdosteine Fudosteine
<b>Nuclear erythroid-2 related factor 2 (Nrf2) activators</b>	Sulforaphane Dimethyl fumarate (BG-12) Bardoxolone methyl CDDO
<b>Catalytic antioxidant enzyme mimetics</b>  <i>Superoxide dismutase (SOD) mimetics</i>  <i>Glutathione peroxidase (GPx) mimetics</i>	Manganese-metalloporphyrin, such as AEOL10113 Manganese-based macrocyclic ligands, such as M40419 Salens, such as EUK-189  Ebselen BXT-51072
<b>Other synthetic small molecule antioxidants</b>  <i>Lipid peroxidation inhibitors</i>  <i>Glutathione</i>  <i>Spin traps</i>  <i>Redox sensors</i>  <i>Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) inhibitors</i>  <i>Myeloperoxidase inhibitors</i>  <i>Inducible nitric oxide synthase (iNOS) inhibitors</i>	Edaravane (MC-186) Lazaroid antioxidant (U-83836E)  Inhaled glutathione  Disufenton sodium (NXY-059)  Thioredoxin mimetics  Nebulized apocynin  AZD3241 INV-315  Non-selective, such as L-NAME Selective inhibitors, such as GW274150
<b>Naturally occurring dietary antioxidants</b>  <i>Polyphenols (phenolic acids and flavonoids)</i>  <i>Vitamins</i>	Resveratrol Green tea catechins/quercetin Curcumin  Vitamin C (ascorbic acid) Vitamin E ( $\alpha$ -tocopherol)

<b><i>Carotenoids</i></b>	$\beta$ -carotene Lycopene
<b><i>Minerals</i></b>	Zinc Selenium
<b><i>Nutritional supplements</i></b>	Acai berry Apocynin Omega-3-fatty acid Acetyl-L-carnitine

Abbreviations: CDDO, the C-28 methyl ester of 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid; L-NAME, L-N(G)-methyl-arginine hydrochloride;

## Figure legend

### Figure 1: Oxidative stress in the pathogenesis of lung damage and comorbidities

Oxidative stress occurs when oxidants overwhelm neutralizing antioxidants due to excess generation of free radicals, termed reactive oxygen species (ROS) and reactive nitrogen species (RNS) and/or due to reduced endogenous antioxidant defences. The generation of ROS occurs from exposure to exogenous factors, such as cigarette smoke, atmospheric pollutants and ionizing radiation and from endogenous sources including inflammatory cells, such as activated macrophages and neutrophils, epithelial cells and by the activation of intracellular oxidative enzymes, such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX2). Increasing generation of ROS and RNS causes depletion of antioxidants. Antioxidant defenses against ROS occurs by the activation of the endogenous enzymes superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) and by non-enzymatic antioxidants that include albumin, mucin and dietary sources, such as vitamins E (tocopherol), vitamin C (ascorbic acid), carotenoids and flavonoids. Excess oxidative stress causes DNA damage, protein carbonylation and lipid peroxidation and these adverse effects are thought to contribute to lung injury in respiratory diseases and the development of systemic comorbidities.

Abbreviations: NO•, nitric oxide; NADPH, nicotinamide adenine dinucleotide phosphate;