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ANTIOXIDANT PHARMACOLOGIAL THERAPIES FOR COPD

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Abstract

Increased oxidative stress occurs in the lungs and systemically in COPD, which plays a role in many of the pathogenic mechanisms in COPD. Hence, targeting local lung and systemic oxidative stress with agents that modulate the antioxidants/redox system or boost endogenous antioxidants would be a useful therapeutic approach in COPD. Thiol antioxidants (N-acetyl-L-cysteine and N-acystelyn, carbocysteine, erdosteine, and fudosteine have been used to increase lung thiol content. Modulation of cigarette smoke induced oxidative stress and its consequent cellular changes have also been reported to be effected by synthetic molecules, such as spin traps (α-phenyl-N-tert-butyl nitrone), catalytic antioxidants (superoxide dismutase [ECSOD] mimetics), porphyrins, and lipid peroxidation and protein carbonylation blockers/inhibitors (edaravone and lazaroids/tirilazad). Pre-clinical and clinical trials have shown that these antioxidants can reduce oxidative stress, affect redox and glutathione biosynthesis genes, and pro-inflammatory gene expression. In this review the approaches to enhance lung antioxidants in COPD and the potential beneficial effects of antioxidant therapy on the course of the disease are discussed.

Keywords

Cigarette smoke; antioxidants; oxidants; glutathione; thiols; Nrf2; Chronic Obstructive Pulmonary Disease

Introduction

The lungs due to their high blood supply and large surface area are constantly in a high-oxygen environment. In addition the lung epithelium is also constantly exposed to oxidants generated endogenously during respiration from mitochondrial electron transport, from activated inflammatory cells that influx into the lungs and exogenously from cigarette smoke (CS) and air pollutants, such as ozone, nitrogen dioxide, and combustion particulates, as a result of its exposure to the environment.

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When the the resident antioxidants are insufficient or fail to upregulate sufficiently to neutralize an increased oxidant burden oxidative stress occurs. Reactive oxygen species (ROS), either non-radical, such as hydrogen peroxide (H_2O_2) or oxygen radicals, such as superoxide anion ($O_2^{\bullet -}$) and the hydroxyl radical (•OH) that are highly unstable species with unpaired electrons are capable of initiating oxidation, and together with reactive nitrogen species (RNS) result in a variety of adverse consequences ranging from cell necrosis, senescence, apoptosis, autophagy, lipid peroxidation and protein carbonylation, inflammatory responses, epigenetic changes, remodeling of extracellular matrix and blood vessels, endothelial dysfunction, inactivation of antiproteases, mucus hypersecretion, and impaired tissue repair [1]. COPD is also a disease associated aging, which has been shown to result in a decline in the endogenous antioxidant defenses resulting in less protection against oxidative stress. The pathogenesis of COPD involves several processes as described above. All of these processes are intimately associated with oxidative stress (Fig 1) [1•].

Rationale for antioxidants therapy in COPD

Cigarette smoke is the main etiological factor in pathogenesis of COPD and contains more than $10^{15\text{-}17}$ oxidant/free radical molecules per puff [2], which increases oxidant burden in the lungs in current smokers. Since many of the pathogenic mechanisms in COPD involve oxidative stress, oxidative stress should be a target for treatment that may have an effect on underlying disease processes in this condition. This could be achieved either by decreasing the generation of oxidants or by enhancing antioxidants.

Clinical testing of several small-molecular weight compounds that target oxidant/redox signaling, or quench oxidants and reactive aldehydes are currently being conducted. Antioxidant agents, such as thiol compounds/donors and their analogs (GSH and mucolytic drugs, such as N-acetyl-L-cysteine, carbocysteine, erdosteine, and fudosteine all effectively scavenge/detoxify free radicals/oxidants, increase intracellular thiol levels and control NF-κB activation, and hence inhibit inflammatory gene expression. Enzyme mimetics that can either enhance the expression/activity of the antioxidant enzymes or mimic their function are currently being developed. In the ensuing sections, we discuss the beneficial effects of a wide variety of pharmacological antioxidants that are potential therapeutic agents in COPD (Table 1). The efficacy of these antioxidant molecules can be assessed by i) improving symptoms or function, ii) modifying the course of the disease by reducing the decline in lung function or decreasing exacerbation frequency, and iii) decreasing the oxidant burden or biomarkers of oxidative stress in patients with COPD.

Small molecule thiol antioxidants

N-acetyl-L-cysteine (NAC)

NAC is an acetyl derivative of the amino acid, cysteine, and is strong reducing agent (Table 1). NAC is a mucolytic agent that reduces mucus viscosity, thereby improving mucociliary clearance. NAC is deacetylated to cysteine in the gastrointestinal tract which serves as precursor of glutathione. By reducing disulfide bonds, NAC is able to neutralize oxidant species. Since NAC can reduce intracellular cystine to cysteine, it can increase intracellular GSH *in vivo* in lungs.

NAC is the most widely studied thiol molecule *in vitro* and *in vivo*. In preclinical studies oral administration of NAC has been shown to attenuate elastase-induced emphysema in rats [3]. NAC also protects against the oxidation of Z α1-antitrypsin by cigarette smoke in an early-onset emphysema mouse model [4]. In view of the importance of glutathione (GSH) as an antioxidant in the lungs, NAC has mainly been used to enhance lung GSH in patients

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with COPD [5]. Clinical studies of the beneficial effects of NAC and other thiols in patients with COPD have yielded mixed results (Table 2) [5-19].

A randomized, double-blind, placebo controlled trial of 6-month of 600 mg NAC, twice daily reduced various plasma and BAL fluid oxidative biomarkers in smokers [18]. NAC 600 mg twice daily for 2 months was shown to reduce the oxidant burden in the airways of stable COPD patients [15], and was associated with reduced risk of exacerbations and improved lung symptoms in patients with chronic bronchitis [10]. Another study has shown a beneficial effect of NAC on muscle function by demonstrating an increase in quadriceps endurance time in severe COPD patients associated with a decrease in markers of systemic oxidative stress [20].

A Cochrane systematic review and other meta-analyses [9] showed a decrease in number of exacerbations by 29% . However, the large multicenter trial, the Bronchitis Randomized on NAC Cost-Utility Study (BRONCUS) showed no effect on exacerbation frequency or decline in FEV_1 [7••]. However, this study showed a reduction in overinflation and in exacerbation frequency in patients with COPD not treated with inhaled glucocorticoids [7].

NAC has to be deacetylated in the gut to cysteine to act as a precursor of GSH and as such is not very bioavailable to increase GSH. Thus further studies may be warranted using NAC at higher doses (1200 or 1800 mg/day) or using other thiol agents that have a greater bioavailability in order to observe any clinical benefit in COPD.

Carbocysteine

S-carboxymethylcysteine (carbocysteine or S-CMC), which has mucoactive, antioxidant and anti-inflammatory properties, is a thiol derivative of amino-acid, L-cysteine (Table 1). Oral preparations of carbocysteine both as S-CMC and its lysine salt (S-CMC-lys) are available. The lysine residue in S-CMC-lys is cleaved in the gastrointestinal tract to yield the active drug S-CMC. The mucoactive action of carbocysteine differs from other thiol mucolytics, such as NAC and erdosteine since it increases the sialomucin content which influences the rheological properties of mucus via the inhibition of kinins [21]. Carbocysteine also facilitates muco-ciliary clearance velocity, particularly in patients with chronic bronchitis who have slow clearance before treatment [21].

In preclinical studies Carbocysteine has been shown to protect against emphysema induced by cigarette smoke in rats [22]. Treatment of COPD patients with S-CMC-Lys for a 6-months significantly decreased the levels of the lipid peroxidation product 8-isoprostane and the pro-inflammatory cytokine: IL-6, indicating that the drug has both antioxidant and anti-inflammatory properties [23].

Due to its ability to reduce bacterial respiratory tract infections in COPD [24-25], it has been suggested that carbocysteine may act via the inhibition of pathogen adherence to cells. This is supported by *in vitro* studies, where carbocysteine treatment has been shown to reduce in the adherence of *Moraxella catarrhalis* (a bacteria commonly found in exacerbations of COPD) to pharyngeal epithelial cells, of both healthy subjects and those with chronic bronchitis, when compared to placebo treated group [24]. Similarly, carbocysteine can significantly reduce attachment of *Streptococcus pneumoniae* to pharyngeal epithelial cells [25]. Carbocysteine could also reduce the frequency of common colds and associated exacerbations in COPD patients, a property that has been attributed to its ability to decrease ICAM-1 expression in the respiratory tract [26].

Clinical studies of carbocysteine in COPD patients are now available (Table 2) [17,26-34]. The PEACE study investigated the effect of treatment of 709 Chinese COPD subjects for 3

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years with carbocysteine (250 mg t.d.s) and found that COPD patients treated with carbocysteine experienced fewer numbers of exacerbations per year [17••]. Of note the majority of these patients were not receiving corticosteroids.

Erdosteine

Erdosteine is a mucoactive thiol antioxidant (Table 1). The drug was originally used as a mucolytic agent and acts by breaking the disulfide bonds of mucus glycoproteins, affecting the physical properties of the mucus, thus leading to increased mucus clearance [35]. It also has antioxidant, anti-inflammatory, and antibacterial activity.

'Equalife', a randomized, placebo-controlled clinical study involving oral administration of 300 mg erdosteine twice daily for 8 months produced a significant improvement in quality of health and a reduction in exacerbations compared to placebo [16]. Erdosteine has also been reported to be beneficial in patients suffering from repeated, prolonged or severe exacerbations of COPD [36-37]. In one study treatment with Erdosteine reduced the rate of severe exacerbations requiring hospital admission [35]. Administration of erdosteine 300 mg twice a day for 7 - 10 days also improved symptoms and reduced the duration of hospitalization in patients presenting with an exacerbation of COPD [38]. Erdosteine (600 mg/day) treatment with procysteine has been shown to improve cigarette smoke-induced ROS production by alveolar macrophages and the levels of the chemotactic cytokines IL-6 and IL-8 in bronchial secretions of current smokers with COPD [37]. The anti-inflammatory properties of erdosteine have also been shown by a reduction in the levels of proinflammatory eicosanoids in blood in COPD patients [39].

Fudosteine

Fudosteine, [(−)-(R)-2-amino-3-(3-hydroxypropylthio)] propionic acid (Table 1), has been used and a mulcolytic and antioxidant. It has greater bioavailability than NAC and acts as an antioxidant by increasing intracellular cysteine levels. In preclinical studies, fudosteine inhibits mucin hypersecretion by downregulating MUAC5AC gene expression [40]. Expression levels of p-p38 MAPK and p-ERK in rat *in vivo* and of p-ERK in a bronchial epithelial cell line *in vitro* are decreased by fudosteine [40]. Fudosteine has also been shown to inhibit peroxynitrite-induced airway nitrative stress in lung epithelial cells by direct scavenging of this free radical [41]. Hence, fudosteine may be used in the treatment of chronic respiratory diseases, such as bronchial asthma, chronic bronchitis, COPD, and bronchiectasis as a mucoactive agent [40,42].

Nrf2 activators

Nuclear factor erythroid 2 p45-related factor 2 (Nrf2) is a basic-leucine zipper (b-ZIP) transcription factor present in the cytoplasm of normal cells that plays an important protective role against electrophiles and ROS. In response to oxidative and electrophilic stresses, Nrf2 detaches from its cytosolic inhibitory subunit, Kelch-like ECH-associated protein 1 (Keap1), and translocates into the nucleus where it binds to the antioxidant response element (ARE) of target genes [43-45]. Nrf2 regulates almost all the antioxidants and phase II cytoprotective genes, such as NAD(P)H/quinone oxidoreductase 1(NQO1), glutamate cysteine ligase modifier subunit (GCLM), glutamate cysteine synthase, glutathione peroxidase (GPx), and several members of the glutathione S-transferase family [43].

Studies with Nrf2 null mice have shown greater susceptibility of these mice to cigarette smoke-induced emphysema compared with wild-type mice [46-47] indicating a protective role for Nrf2. Loss of Nrf2 positive regulator DJ-1 (stabilizer of Nrf2) and posttranslational modifications of the Keap1–Bach1 equilibrium results in downregulation of Nrf2 in the

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lungs of patients with COPD [48-51•]. The Nrf2 activator CDDO-imidazolide (Table 1) has been shown to protect mice against CS-induced emphysema [45•]. Activation of Nrf2 by sulforaphane (present in broccoli and cruciferous vegetables) can also have a beneficial effect in attenuating some of biochemical alterations that occur in smokers/COPD [52••].

Novel compounds which are potent activators of Nrf2 or which stabilize Keap1/DJ-1/Maf proteins can be developed. Chalcones have anti-inflammatory effects due to their ability to inhibit the NF-κB pathway [53-54] and simultaneously activate the Nrf2/ARE pathway thus inducing phase II detoxifying enzyme expression [55]. Currently, various derivatives of chalcones are being developed with a potential therapeutic role in COPD [56•]. However, the pharmacokinetics, bioavailability, and toxicity of these compounds in the lungs are as yet unknown.

Lipid peroxidation and protein carbonylation inhibitors/blockers

Edaravone (MC-186)

Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) is a potent free-radical and protein carbonyl scavenger and inhibitor of lipid peroxidation [57-58]. Protein carbonylation and carbonyl stress via aldehydes occur in COPD and hence edaravone has the potential to protect the lungs against the effects of these oxidative products [59-60]. Edaravone has been shown to ameliorate the lung injury, inflammation, oxidative stress, and mortality induced by intestinal ischemia/reperfusion in rats [61]. Given the antioxidant, anti-inflammatory properties of edaravone, it has potential as a treatment in COPD.

Lazaroids

Lazaroids (21-aminsteroids, U75412E or tirilazad mesylate) are a group of non-glucocorticoid analogues of methyl-prednisolone which are able to penetrate hydrophobic regions of the cell membrane, specifically to prevent peroxidation of membrane lipids [62]. The protective effects of lazaroids have been reported in many animal models of lung injury [63-64], including the effects of cigarette smoke [65]. Their protective effect is mainly by inhibition of lipid peroxidation. In a smoke-induced lung injury model lazaroids inhibited the formation of free radicals and the release of tumor necrosis factor-α by alveolar macrophages [66-67]. Further studies are required to evaluate the efficacy of lazaroids as therapeutic strategy in COPD.

Enzymatic antioxidants

Cellular ROS can be effectively neutralized by antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, whose expression and activities are altered in various disease conditions involving oxidative stress. Restoration of altered antioxidant enzyme activity can be achieved by small molecules possessing catalytic properties which can mimic the activity of the enzyme.

SOD mimetics

SOD mimetics are of three classes. The first class includes several manganese-based macrocyclic ligands, such as M40401, M40403, and M40419 [68-69]. The second class includes manganese-metaloporphyrins, such as AEOL-10113 and AEOL-10150 [70-71], and the third category is comprised of “Salens” (manganese based SOD mimetic). Salens have an additional advantage as they are also reported to have catalase-like activity, and therefore can also neutralize H_2O_2, and $ONOO^-$ [72]. Until now only the second class of SOD mimetics has been studied in animal models of airway inflammation. A significant decrease in the lungs of markers of oxidative stress, and emphysema has been observed in response to the SOD mimetic M40419 in animal models [68]. The SOD mimetic

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AEOL10150 has also been shown to inhibit cigarette smoke-induced lung inflammation in the rat and to decreased lipid peroxidation and the generation of $ONOO^-$ [71]. The ability of recombinant SOD treatment to prevent neutrophil influx into the lungs and decrease IL-8 release induced by cigarette smoking [73], indicates its potential as an antioxidant an anti-inflammatory in COPD.

Broad antioxidant properties and the ability to scavenge superoxide, lipid peroxides, ONOO-, and H_2O_2 have been attributed to the metalloporphyrin-based catalytic antioxidant, MnTE-2-PyP [Manganese (III) Meso-Tetrakis-(NMethlypyridinium-2-yl) porphyrin] [74-76]. Administration of MnTE-2-PyP has been shown to decrease inflammation and injury induced by wide variety of factors [77-78]. Its anti-inflammatory properties have been attributed to its ability to reduce NF-κB signaling [77]. Therefore, these compounds may have potential for therapeutic use in COPD.

Extracellular superoxide dismutase (ECSOD or SOD3) is highly expressed in lungs and is located in the extracellular matrix in the junctions of airway epithelial cells, the surface of airway smooth muscle, and the lining of blood vessels of the lungs [79]. SOD3 directly scavenges $O_2^{\bullet-}$, and may therefore play an important role in protecting against oxidative lung damage. SOD3 protects against cigarette smoke/elastase induced mouse models of emphysema via reduction of oxidative ECM fragmentation and oxidative posttranslational modifications of elastin fragments (leading to autoantibody production) [80••]. A recent study has revealed that SOD3 can decrease CS-induced oxidative stress in mouse macrophages [81]. SOD3 also attenuates lung inflammation and emphysema by decreasing oxidative fragmentation of ECM, such as heparin sulfate and elastin [80]. Therefore, the development of pharmacological mimetics to replenish/augment SOD3 in the lung would be a rational therapeutic intervention for COPD/emphysema.

Glutathione peroxidase (GPx) mimetics

Ebselen is a selenium-based organic complex that mimics the activity of glutathione peroxidase. Ebselen is strong antioxidant and is also known to have strong neutralizing effect against the peroxynitrite radical [82]. Ebselen inhibits the activation of NF-κB/AP-1, and hence the expression of pro-inflammatory genes in human leukocytes treated with peroxynitrite. Ebselen has been shown *in vivo* in animal models to prevent LPS-induced airway inflammation [83-84]. However, no reports are available as the protective effect of ebselen against cigarette smoke-induced lung inflammation.

Spin traps and iNOS inhibitors

Spin traps are chemical agents which can quench free radicals to form measurable stable end products. Most spin traps have a nitrone- or nitroxide-nucleus and are derivatives of these moieties. Spin traps have been widely used for *in vitro* studies and their therapeutic effects *in vivo* have also been investigated in models of lung inflammation using α-phenyl-N-tert-butyl nitrone [85]. Early spin traps had extremely small half lives and generated toxic hydroxyl radicals on decay. This problem has now been overcome by the introduction of electron withdrawing moieties around the core pyrroline ring [86]. Isoindole-based nitrones [87] and azulenyl-based nitrones [88], such as STANZ have strong antioxidant properties and can inhibit lipid peroxidation *in vitro*. Phenyl-base nitrone spin trap (PBN) derivatives, such as NXY-059 (PBN-2,4,disulfonate), have been shown to have benefits in a wide variety of animal models of lung diseases (http://www.nitrone.com/).

Recent studies have suggested that inhibition of iNOS by various chemical inhibitors [N(6)-(1-iminoethyl)-L-lysine (L-NIL), G-nitro-L-arginine-methyl ester or L-NAME attenuated animal models of emphysema [89-91]. It is possible that selective inhibition of iNOS [90•]

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along with supplementation of other antioxidants may provide a strategy in the management of COPD.

Redox sensors: Enzymatic

Thioredoxin

Thioredoxin (Trx) and redox effector factor-1 (Ref-1), belong to oxidoreductase family of redox sensors. Trx, is primarily bound to proteins, such as hepatopoietin [92] and the apoptosis signal regulating kinase (ASK-1) [93], that are released from these complexes during oxidative stress [92]. After dissociation, Trx reduces a key thiol group within the p65/NF-κB subunit leading to transcriptional activation [94]. Inhibiting Trx (in the nucleus) with MOL-294 (a small molecular weight inhibitor of Trx), blocks nuclear activation of both NF-κB and AP-1-dependent transcription that results in diminished neutrophil influx and TNF-α production in an animal model [95]. Activation of Trx by synthetic small molecules attenuated oxidative stress [96]. Overexpression of thioredoxin-1 (Trx-1), primarily due to its antioxidant property attenuates CS-mediated oxidative stress and emphysema [97•], however the effects in COPD still remain to be investigated.

Conclusions

Increased oxidative/carbonyl stress occurs in COPD as is thought to be an important mechanism in the pathogenesis of this condition. Targeting oxidative stress with pharmacological antioxidants or boosting the endogenous levels of antioxidants is likely to be beneficial as a treatment in COPD. Antioxidant therapy may affect important outcomes in COPD, such as overcoming steroid resistance, mucus hypersecretion, inflammation, and ECM remodeling. Several small molecule antioxidant compounds have been investigated in pre-clinical and clinical trials. Although thiol antioxidant treatments have shown promising effects in targeting ROS and adverse oxidant-mediated cellular responses, development of novel wide-spectrum small molecule antioxidants with a good bioavailability and potency are needed for clinical trials for COPD. However, the clinical trials have been limited and there is a lack of information on pharmacokinetics, bioavailability, toxicity, and absorption of various exogenous antioxidants and activators of endogenous antioxidants.

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Highlights

Cigarette smoke causes oxidative stress in COPD.

Antioxidants can modulate intracellular redox system.

Thiols, enzyme mimetics, spin traps, and redox sensors are therapeutic agents.

Lipid peroxidation and protein carbonylation inhibitors block oxidative processes.

Antioxidants have pharmacological beneficial effects in management of COPD.

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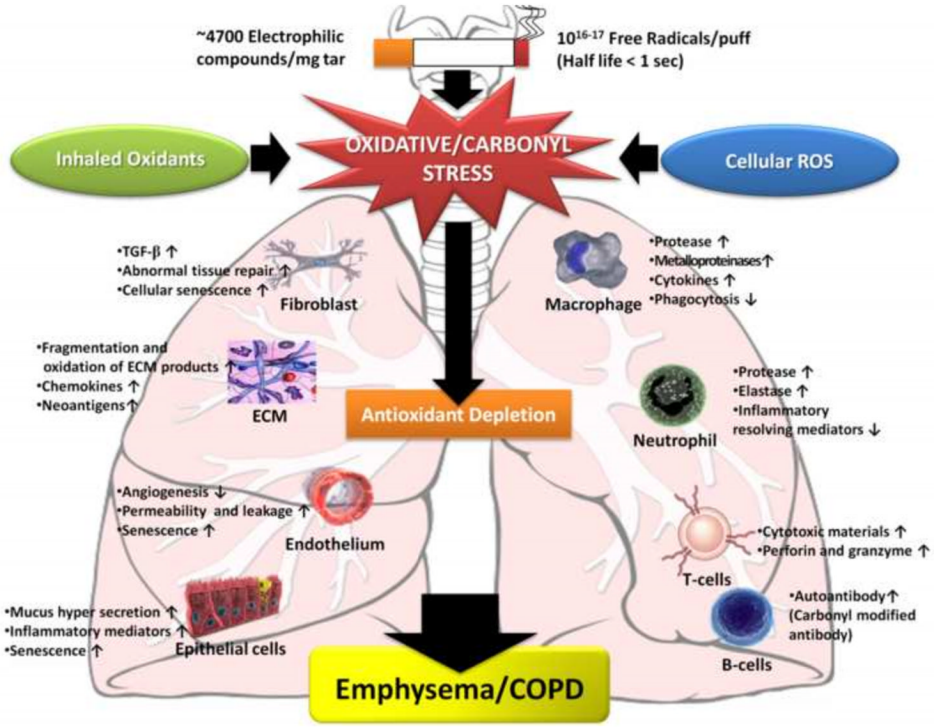

Figure 1. Consequences of oxidative stress in COPD

The pathogenesis of COPD involves several oxidative stress-induced cellular and molecular processes. Oxidative stress imposed by inhaled oxidants or produced from endogenous sources can lead to depletion of antioxidants. An oxidant/antioxidant imbalance in favor of oxidants leads to activation of various cellular processes which result in cellular and molecular events involved in pathogenesis of COPD.

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Table 1

A list of thiol antioxidants and Nrf2 activators

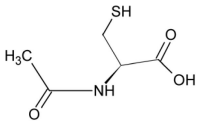
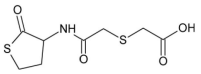
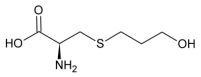
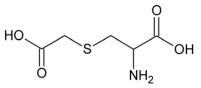
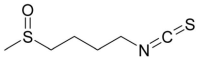
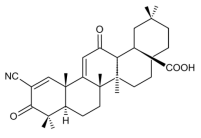
Antioxidant	Structure
N-acetyl-L-cysteine	
Erdosteine	
Fudosteine	
Carbocysteine (*S*-Carboxymethyl-L-cysteine)	
Sulforaphane	
Triterpenoids- 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) Other analogs of CDDO -1[2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole (CDDO-Im) Dihydro-CDDO-Trifluoroethyl Amide CDDO Methyl Amide	

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Table 2

Clinical trials conducted for the efficacy of thiol antioxidants in smokers and COPD

Clinical Trial	Antioxidant	Study Aim	Outcome	Reference
BRONCUS	NAC	Effect of NAC on FEV_1	No effect. A reduction in lung over inflation in patients with severe COPD without inhaled glucocorticoids No change on decline in FEV_1. Decrease of exacerbation if NAC and Inhaled corticosteroids combined.	[6-7]
Systematic Cochrane review of 23 randomized, controlled trails	NAC (2 months of oral therapy)	Effect of NAC and antibiotics on number of days of disability	No difference in lung function. Significant reduction in days of disability (0.65 day per patient per month) and 29% reduction in exacerbations.	[8-9]
Systematic Cochrane review of randomized, controlled trials; 11 of 39 retrieved trials	NAC	Use of validated score to evaluate the quality of each study	9 trials showed prevention of exacerbation and 5 of which addressed improvement of symptoms compared with 34.6% of patients receiving placebo.	[10]
Meta-analysis of published trials	NAC	Assess possible prophylactic benefits of prolonged treatment	23% decrease in number of acute exacerbations	[11]
-	NAC (600 mg/d, 5 days and 600 mg, 3/d. 5days)	Effect of NAC on GSH and cysteine	Increase of GSH at day 5 and cysteine (plasma) at day 5	[5]
-	NAC (600 mg once a day for 12 months)	Effect of NAC on H_2O_2 and TBARS in EBC	No change in TBARS levels Reduce H_2O_2 levels	[12]
-	NAC (600 mg/d, 7days)	Effect of NAC on FEV_1, breathlessness	No difference compared to placebo group	[13]
-	NAC (600 mg /d)	Effect of NAC on cytokine and exhaled breath condensate (EBC)	Decrease IL-8 and ECP level in NAC group	[14]
-	NAC (600 mg × 2/d × 2 months)	Effect of NAC on H_2O_2	Decrease H_2O_2 level in NAC group	[15]
EQUALIFE studies	Vectrine-thiol compound, 300mg b.i.d for months	Effect on exacerbation rate, hospitalization, lung function and quality of life	Decreased exacerbations and fewer days in hospital. No loss of lung function and improvement in health-related quality of life.	[16]
Small scale UK studies	Carbocysteine	Effect of 2.25–3.00 g carbocysteine daily along with placebo in chronic bronchitis	Heterogeneous results on alterations in FEV_1, peak flow rate and dyspnea scores	[27-30]
An Italian multi-center, prospective, double-blind RCT involving 662 outpatients with a chronic	Carbocysteine	Effect of 2.7 g S-CMC-Lys once daily for 6 months on COPD patients	No significant difference in baseline FEV_1 between the groups. Mean time to first exacerbation was significantly prolonged and significant reduction in mean days of acute	[31]

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Clinical Trial	Antioxidant	Study Aim	Outcome	Reference
bronchitis			respiratory illness per patient.	
A double–blind, parallel-group study in the UK in 109 patients with chronic bronchitis over 6 winter months	Carbocysteine	Effect of 750 mg carbocysteine three times daily compared with placebo on peak flow and exacerbation rate.	No significant difference in exacerbation rate. Significant increases in peak flow from baseline in both placebo and intervention groups	[32]
RCTs in Tokyo in 156 patients with COPD over a 12-month period	Carbocysteine	Effect of 1.5 g carbocysteine daily with placebo	No significant differences in severity of COPD. Significant reduction in the number of common colds and reduction in rate of exacerbation	[33-34]
RCTs in Japan involving 142 patients with COPD conducted over a 12-month period	Carbocysteine	Treatment with 500mg carbocysteine three times a day	Consistent reduction in exacerbation frequency. No change in lung function	[26]
PEACE study EQUALIFE studies	Carbocysteine (carbocisteine) Vectrine-thiol compound, 300mg bid for months	Effect on rate of exacerbations Effect on exacerbation rate, hospitalization, lung function, and quality of life	Long-term (one year) use of carbocysteine (1500 mg/day) produced reduction in numbers of exacerbations in patients with COPD Decreased exacerbations and fewer days in hospital. No loss of lung function and improvement in health-related quality of life	[17] [23]

BRONCUS = Bronchitis Randomized on N-acetyl-L-cysteine Cost Utility Study, bid= Twice daily; FEV_1 = Forced expiratory volume in 1 second, TBARS = Thiobarbituric acid reactive substances, *NAC* = N-acetyl-L-cysteine, *EBC* = Exhaled Breath Condensate, RCTs: Randomized placebo-controlled trials.