

## The Role of ROS in COPD Progression and Therapeutic Strategies

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**ABSTRACT** | The atmosphere is replete with a mixture of toxic substances. Inhalation of toxic substances produces a variety of insults on the pulmonary system. Lung poisons include industrial materials and a large number of environmental contaminants. This review will give an in-depth knowledge of how the development and progression of chronic obstructive pulmonary disease (COPD) are associated with increased oxidative stress or reduced antioxidant resources. It has been documented that several indicators of oxidative stress, such as hydrogen peroxide exhalation, lipid peroxidation products, and degraded proteins, are indeed elevated in COPD patients, and as a result, the antioxidant capacity decreases. The fall in antioxidant capacity of blood from COPD patients should not only be regarded as a reflection of the occurrence of oxidative stress but also as evidence that oxidative stress spreads out to the circulation and can therefore generate a systemic effect. An effective wide-spectrum antioxidant therapy that has good bioavailability and potency is a good approach to redressing the lungs antioxidant capacity to control the localized oxidative and inflammatory processes that occur in the pathogenesis of COPD.

**KEYWORDS** | Chronic obstructive pulmonary disease; Oxidative stress; Reactive oxygen species

**ABBREVIATIONS** | AAT1, alpha-1 antitrypsin; BAL, broncho-alveolar lavage; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in the first second of a forced exhalation; GSH, reduced form of glutathione; 4-HNE, 4-hydroxynonenal; MDA, malondialdehyde; MPO, myeloperoxidase; MSI, microsatellite DNA instability; NO, nitric oxide; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; VEGF, vascular endothelial growth factor; XO, xanthine oxidase

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## 1. INTRODUCTION

All life forms maintain a reducing environment within their cells, which is preserved by enzymes that maintain the reduced state through a constant input of metabolic energy. Any disturbances in this normal redox state can cause toxic effects through the production of peroxides and free radicals, better known as reactive oxygen species (ROS) that damage all components of the cell, including proteins, lipids, and DNA [1]. ROS and reactive nitrogen species (RNS) are reactive products required by the body for both beneficial and deleterious purposes. In the cells, their production in balanced amounts is essential for maintaining normal physiological functions [2]; however, sometimes when produced in excess, they result in damage to tissues unless regulated by an antioxidant system.

ROS-mediated oxidative stress is known to play an important role in pathogenesis of chronic obstructive pulmonary disorder (COPD), since it results in inactivation of antiproteinases, induces airspace epithelial injury, mucus hypersecretion, increased influx of neutrophils into the lungs, transcription factor activation, and gene expression of pro-inflammatory mediators [3]. COPD affects about 6% of the general world population and is the leading cause of morbidity and mortality worldwide [4]. China and India are bearing a disproportionate burden of COPD morbidity and mortality. Since both countries together constitute one third of worldwide humanity, burden of COPD would have considerable impact on their economy. Worldwide only 10–15% of all cases are identified medically, out of which about 1% is attributed to alpha-1 antitrypsin (A1AT) [5]. The central

Indian population has seen a large influx of patients with respiratory complaints having obstructive and restrictive respiratory functions in the past decade [6, 7] resulting in additional economic burden on the society.

## 2. COPD—A DISEASE HAND IN HAND WITH OXIDATIVE DAMAGE

COPD is a heterogeneous disorder resulting in dysfunction of the small and large airways, and destruction of lung parenchyma and vasculature. In a healthy individual, the lower airways are sterile, and in order for microorganisms (bacteria/viruses) to reach the lungs, they must pass through the upper airway first. Surprisingly, research on microbial colonization in patients with COPD exacerbations has found no potentially pathogenic microorganism but normal respiratory flora responsible for progression in the disease state [8]. The lungs, compared to other organs, are highly vulnerable as they are directly exposed to high levels of oxygen from the atmosphere. Consequently, respiratory epithelium is a major target for oxidative injury from oxidants generated either exogenously (cigarette smoke/toxic pollutants) or endogenously (from phagocytes and other cell types). Thus, the lungs are rich in efficient enzymatic and non-enzymatic antioxidant defense systems to protect themselves from oxidant-induced damage [9] (**Figure 1**). If the balance between oxidants and antioxidants shifts in favor of the former, it would result in airway tissue inflammation, airway limitation, and mucus hypersecretion. In COPD, oxidant stress occurs in small airways, lung parenchyma, and alveolar

regions, and is associated with the activation of cytokines and growth factors and activated inflammatory cells that produce large amounts of ROS and RNS. Most of the ROS and RNS produced in the lung tissue come from neutrophils, alveolar macrophages, and eosinophils, but bronchial and alveolar epithelial cells and endothelial cells are also capable of producing ROS [10].

Based on genotype-environment interactions, Wood and Stockley [11] have defined COPD pathogenesis according to clinical phenotypes thus influencing the risk of acquiring the disease at different levels. According to them, there are three main theories suggesting COPD pathogenesis: (1) the protease-anti-protease theory, stating that there is an imbalance between proteases that digest elastin, together with other components of the extracellular matrix, and anti-proteases that protect against this; (2) the oxidant-antioxidant theory, stating that disparity between levels of harmful oxidants and protective antioxidants leads to oxidative stress, which in turn influences the actions of anti-proteases, and the expression of proinflammatory mediators; and (3) the importance of inflammation in the pathogenesis of COPD. The first two theories are in fact linked to the third one. Polymorphisms in genes relating to proteases, antioxidants, and inflammation have been found that relate to the presence of features of COPD, suggesting reasons for the heterogeneity of the observed clinical phenotypes.

### 3. ROS AND THEIR SOURCES

ROS are produced by living organisms as a result of normal cellular metabolism. At low to moderate concentrations, ROS function in physiological cell processes, but at high concentrations, they create undesirable effects. COPD is a progressive disease which manifests itself slowly and gradually. The pathogenesis of COPD apart from oxidative stress, inflammation, and protease/antiprotease imbalance also involves alteration in immunity (autoantibody production), apoptosis, alteration of cell proliferation, and cellular senescence/aging, induced by air pollutants, modified by genetic factors, and exacerbated by viruses and bacteria [12]. Prevalence of acquiring this disease is doubled in elderly people than at younger age, and thus COPD is known as an aging associated disease. The evidence for the role of ac-

celerated aging in COPD progression is senescence [13]. As suggested in the “free radical theory of aging” [14], ROS account for progressive deleterious changes called aging or senescence. This results in accumulating modifications in cell components, such as lipids, proteins, and DNA [15], and imbalance between oxidants and antioxidants resulting in oxidative stress [16].

#### 3.1. Cell-Derived ROS

Various sources can generate ROS intracellularly in a metabolically active cell. The chief ROS-generating enzyme is NADPH oxidase, which is present in phagocytes and epithelial cells. Phagocytes employ NADPH oxidase and other enzymes to produce ROS, which further involve the activity of heme peroxidases, such as myeloperoxidase (MPO) and eosinophil peroxidase (EPO). The oxidative stress derived from MPO plays an important role in the pathogenesis of COPD. Superoxide anion and  $H_2O_2$  can also be generated by mitochondria and the xanthine/xanthine oxidase (XO) reaction. XO activity has been shown to be increased in cell-free broncho-alveolar lavage (BAL) fluid and plasma from COPD patients, compared with normal individuals [17]. RNS in the form of nitric oxide (NO) production is generated by nitric oxide synthase in the same manner. Similarly, NO forms the more effectual and damaging peroxynitrite molecules in the presence of superoxide anion [18].

#### 3.2. Environmental Sources of ROS

Cigarette smoke contains many oxidants and free radicals and organic compounds, such as superoxide and nitric oxide [19]. Inhalation of cigarette smoke activates certain endogenous mechanisms in the lung, such as accumulation of neutrophils and macrophages, which further increase oxidant injury. Ozone exposure can cause lipid peroxidation and induce influx of neutrophils into the airway epithelium. Short-term exposure to ozone also causes the release of inflammatory mediators, such as MPO and eosinophil cationic proteins along with lactate dehydrogenase and albumin [20]. Ozone exposure also results in reduction in pulmonary functions even in healthy subjects [21] developing conditions like hyperoxia—higher oxygen levels than normal partial pressure of oxygen in the lungs or other body tis-

sues—that lead to greater production of ROS and RNS [22, 23].

Ionizing radiation, in the presence of O<sub>2</sub>, converts hydroxyl radicals, superoxide, and organic radicals to hydrogen peroxide and organic hydroperoxides. These hydroperoxide species react with redox active metal ions, such as iron and copper via Fenton reactions and thus induce oxidative stress [24, 25]. Heavy metal ions, such as iron, copper, cadmium, mercury, nickel, lead, and arsenic can bring on generation of reactive radicals and cause cellular damage via depletion of enzyme activities through lipid peroxidation and reaction with nuclear proteins and DNA [26].

There is evidence that accidental exposures to noxious chemicals like isocyanates can induce DNA damage, apoptosis, inflammation, and oxidative stress [14], and such victims with evidence of residual lung damage might run a clinical course similar to COPD with recurrent respiratory illnesses [27].

#### 4. CONSEQUENCES OF OXIDATIVE STRESS—LIPID PEROXIDATION

In biological systems, phospholipids in cell membrane can be hydrolyzed by the phospholipase enzyme, producing nonesterified arachidonic acid that undergoes peroxidation through two pathways: (1) the enzymatic pathway, involving cyclooxygenases and lipoxygenases; and (2) a non-enzymatic pathway through the participation of ROS, RNS, transition metals, and other free radicals [28]. ROS can activate the peroxidation of polyunsaturated fatty acids in biological tissues resulting in the transformation of the fatty acids into lipid hydroperoxides. Lipid peroxides and lipid hydroperoxides can then interact with enzymatic or nonenzymatic antioxidants or decompose after reacting with metal ions or iron-containing proteins, forming hydrocarbon gases and unsaturated aldehydes as byproducts [29].

The hydrocarbon ethane is another byproduct of fatty acid peroxidation. Patients with COPD display an increased level of exhaled ethane compared to control subjects. This increased level is negatively correlated with lung function, suggesting that lipid peroxidation is an important factor in the progression of COPD [30, 31]. Furthermore, the lungs are also involved in the elimination of ethane transported from other organs such as intestine, brain, kidney,

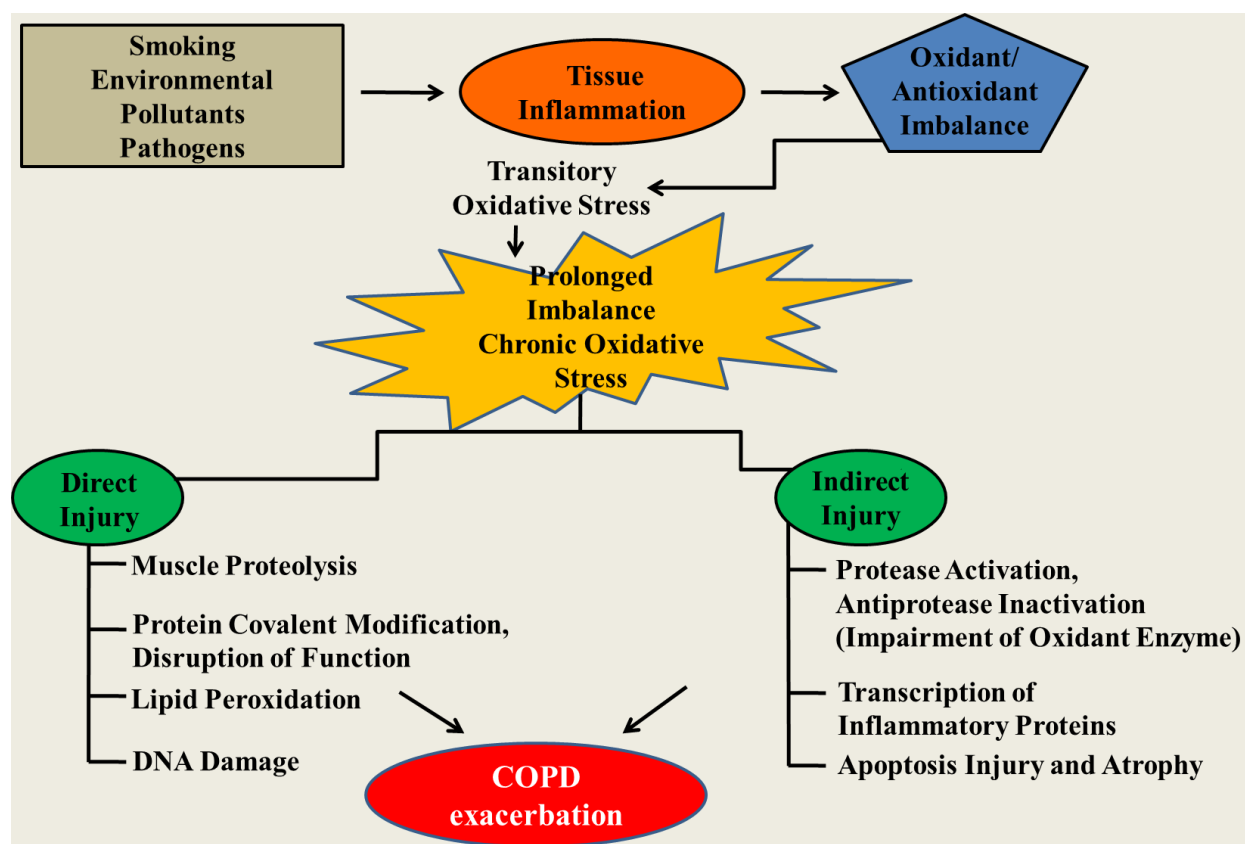
liver, heart, and testes. Therefore, it is suggested that the systemic oxidative stress in smokers and COPD patients may contribute to the total exhaled ethane concentration [32].

#### 4.1. Oxidative Stress and Protein Modification

ROS can cause crumbling of the peptide chain, modification of electrical charge of proteins, cross-linking of proteins, and oxidation of specific amino acids and therefore lead to increased susceptibility to proteolysis by precise proteases [33]. These oxidative modifications can inactivate the enzymatic functions and cause structural degeneration of the proteins or activate transcription factors and proteolytic systems. Paster and coworkers [34] in their study have identified differential proteomic profiles related to oxidative stress response in COPD patients. Indeed, human plasma proteins are indeed modified to carbonyl-containing proteins with lost sulfhydryl groups after exposure to gas phase cigarette smoking [35]. Both saturated and unsaturated aldehydes present in cigarette smoke contribute to this modification of proteins. Additionally, exposure of human plasma to cigarette smoke in vitro also results in depletion of plasma protein sulfhydryls and elevation of the carbonyl protein levels [36, 37]. Plasma proteins can also be degraded through nitration and oxidation by RNS, the formation of which is stimulated by cigarette smoking [38]. Levels of oxidised proteins are significantly higher in smokers than in non-smokers [39].

#### 4.2. Oxidative Stress and Inflammation

The role of ROS in generating inflammatory response occurs in both central and peripheral airways of COPD patients [38, 40]. A common attribute of lung inflammation is the activation of epithelial cells and resident macrophages as well as activation of neutrophils. Oxidants in cigarette smoke are capable of stimulating alveolar macrophages thus releasing a number of mediators, attracting neutrophils and other inflammatory cells into the lungs inflammatory response [38, 41]. Increased numbers of both macrophages and neutrophils migrate into the lungs of smokers generating ROS via NADPH oxidase system [41, 42]. The MPO content of the neutrophils is certainly linked with cigarette smoking, suggesting an increased production of oxidants like hypochlo-



**FIGURE 1.** Schematic representation depicting oxidative injury to the lung tissue leading to COPD exacerbations. See text for detailed description. COPD denotes chronic obstructive pulmonary disease.

rous acid in smokers [43]. A relationship has been shown between the circulating neutrophil numbers and the FEV1 (forced expiratory volume in the first second of a forced exhalation) [44, 45], suggesting decreased airflow as a result of the ROS production. Smokers who develop COPD have increased ROS release from the circulating neutrophils compared to smokers who do not develop the disease [46].

Under physiological conditions, the control of redox-sensitive signaling involves temporary deviation from the redox state toward an increase in the concentration of oxidants. These small oxidative episodes generate low cellular concentrations of ROS when stimulated by cytokines (IL-1, IL-6, IL-3, and TNF- $\alpha$ ), angiotensin II, and growth factors. The signals for the elements responsible for the expression of certain genes are normally transmitted to the nucleus by a class of proteins known as transcription

factors. This process of signaling transduction results in biological functions such as muscle contraction, gene expression, cell growth, and nervous transmission. Therefore, the initiation and correct functioning of various transduction pathways depend on ROS as signaling molecules, which act as second messengers [47]. Under pathological conditions, however, abnormally high concentrations of ROS in the cells might lead to permanent changes in signaling transduction and gene expression, as observed in chronic inflammatory diseases, including COPD [48].

#### 4.3. Oxidative Stress and Apoptosis

Data mining of recent studies has highlighted the importance of apoptosis in the pathogenesis of COPD [49, 50]. There is evidence that vascular endothelial growth factor (VEGF) is necessary for the



maintenance of the cellular structure of the lungs [51]. The interruption of the VEGF signalling to VEGF receptor 2 results in arrested lung development, which manifests clinically as bronchopulmonary dysplasia in children and as emphysema in adults [52].

It has recently been reported that oxidative stress is associated with a reduction in the levels of VEGF in the sputum of patients with COPD. It has been suggested that oxidative stress can lead to epithelial cell damage, thus reducing VEGF levels and consequently favoring the development of emphysema [53]. Another mechanism that has been reported in inducing apoptosis through oxidative stress is the activation of certain mitochondrial enzymes, including caspase-3 [50].

#### 4.4. Oxidative Stress and Protease-Antiprotease Imbalance

Three classes of proteases are considered relevant to the etiopathogenesis of COPD. They are: (1) serine proteases, which can degrade elastin and certain forms of collagen; (2) cysteine proteases, which degrade matrix components; and (3) matrix metalloproteinases, which act on collagen, gelatin, and laminin. Each of these classes of enzymes can be inhibited by one or more antiproteases. Oxidants can potentiate the effects of proteases on COPD through activation of these enzymes. Reactive species increase the activity of matrix metalloproteinases by activating metalloproteinase precursors. The oxidation of methionine residues at active sites of alpha-1 antitrypsin (AAT1) results in a dramatic reduction in its *in vitro* inhibitory ability. Therefore, this pathway has been reported as one of the possible causes of the imbalance in favor of proteases [49, 50]. In COPD, the protease burden in the lungs is increased because of the influx and activation of inflammatory leukocytes that release proteases. It has been proposed that a relative deficiency of antiproteases such as AAT1, because of their inactivation by oxidants, creates a protease-antiprotease imbalance in the lungs. This hypothesis forms the basis of the protease-antiprotease theory of the pathogenesis of emphysema [54, 55].

Inactivation of AAT1 by oxidants occurs at a critical methionine residue in its active site and can be produced by oxidants from cigarette smoke or oxidants released from inflammatory leukocytes, result-

ing in a marked reduction in the inhibitory capacity of AAT1 *in vitro* [55, 56]. An *In vivo* study of the acute effects of cigarette smoke on the functional activity of AAT1 shows transient but non-significant fall in the antiprotease activity of BAL fluid shortly after cigarette smoking [57]. In addition, *in vitro* exposure of lung epithelial cells to proteases leads to increased release of ROS, suggesting that proteases increase oxidative stress [58].

#### 5. SYSTEMIC OXIDATIVE STRESS ESPECIALLY INVOLVING THE LUNGS—COPD EXACERBATIONS

COPD is considered to have local lung and systemic effects [59]. Decreased peripheral muscle function and weight loss leading to reduced survival are the main evidence of systemic effects [60]. Increased sequestration of neutrophils in the pulmonary circulation during smoking and during exacerbations of COPD is also an oxidant-mediated event [61]. Many studies have shown an inverse relationship between circulating neutrophil numbers and FEV1 [44, 45]. Moreover, a similar relationship has also been shown between the change in peripheral blood neutrophil count and the change in airflow limitation over time [62]. Similarly, an association between superoxide anion release by peripheral blood neutrophils and bronchial hyperresponsiveness in patients with COPD has been seen, suggesting a role for systemic ROS in the pathogenesis of airway abnormalities in COPD [63].

Cigarette smoking increases the formation of RNS and results in nitration and oxidation of plasma proteins. The levels of nitrated proteins (fibrinogen, transferrin, plasminogen, and ceruloplasmin) were higher in smokers when compared with non-smokers. The levels of nitrotyrosine along with inducible NO synthase (iNOS) were higher in airway inflammatory cells obtained by induced sputum from patients with COPD compared with those with asthma [64].

Systemic markers of oxidative stress and elevated plasma levels of inflammatory mediators have been reported in smokers and in patients with COPD [65, 66]. Lipid peroxidation products are also increased in the plasma of smokers with COPD, particularly in state of exacerbation. Oxidative stress and chronic inflammation are some of the factors involved in the

mechanism that generates the systemic manifestations (e.g., weight loss and skeletal muscle dysfunction) observed in some patients with COPD. Patients with COPD are also at increased risk of cardiovascular disease and one of the probable mechanisms for this increase is the endothelial damage caused by systemic inflammation and systemic oxidative stress in these patients [67].

### 5.1. Biomarkers for COPD

COPD is irreversible and known to get exaggerated due to smoking. However, not all smokers develop clinically relevant COPD. Thus, variable response to cigarette smoke clearly suggests genetic susceptibility. Among the COPD candidate genes are those that: (a) affect the production of proteases and antiproteases; (b) modulate the metabolism of toxic substances in cigarette smoke; (c) are involved in mucociliary clearance; and (d) influence inflammatory mediators. Recently, microsatellite DNA instability (MSI)-positive sputum cells from smokers with and without COPD have been found to be a useful marker of genetic susceptibility. Nevertheless, COPD lacks established viable biomarkers to predict and monitor disease progression and outcome variations. Such monitoring tools may be induced sputum, exhaled air condensate, peripheral blood, urine, bronchial biopsies, and BAL fluid [68].

### 5.2. Oxidative Stress Biomarkers in Exhaled Breath Condensate

Oxidative stress can be measured through direct quantification of the production of oxidants or, indirectly, through quantification of the products resulting from lipid peroxidation, such as 8-isoprostane, 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) in the alveolar space, exhaled air, sputum, and blood [69].

Recent studies have focused on non-invasive techniques, such as biomarkers in exhaled breath condensate to evaluate oxidative stress in COPD [70, 71]. The collection of exhaled breath condensate (EBC) is a non-invasive method for obtaining samples of material from the lower respiratory tract. Non-specific lipid peroxidation products, such as thiobarbituric acid reactive substances (TBARS), have also been shown to be elevated in breath condensate and in the lungs of patients with stable

COPD [72]. Other specific products of lipid peroxidation such as MDA and 4-HNE have also been shown to be greater than before in exhaled breath condensate of COPD patients [72, 73].

Among the indirect measures for assessing oxidative stress is an examination of the increased activity of the heme oxygenase system, which is reflected by the carbon monoxide levels in exhaled breath. Assessment of the effects of oxidative stress on target molecules may include measuring the reaction of ROS with lipids, proteins, or nucleic acids to form markers of oxidative stress. These markers can be measured in the blood, breath condensate, BAL fluid, and lung tissue as an indicator of the effects of free radicals on target molecules [74].

### 5.3. Antioxidant Defense in COPD

Under normal condition, the lungs have well coordinated and efficient endogenous antioxidant defense systems, which protect against the injurious effects of oxidants by electron transfer, enzymatic removal, and scavenging, and by keeping transition metal ions tightly sequestered [75]. Dietary antioxidant supplementation is one of the simplest approaches to boosting antioxidant defence systems. Supplementation of vitamin C, vitamin E, and  $\beta$ -carotene has been attempted in cigarette smokers and patients with COPD [31]. Dietary polyunsaturated fatty acids may also protect cigarette smokers against the development of COPD [76]. These studies support the concept that dietary antioxidant supplementation including polyphenols may be a possible therapy to prevent or inhibit oxidative stress and inflammatory responses, which are key features in the development of COPD. The most direct way to redress the oxidant imbalance in COPD would be to increase the lung's capacity to produce antioxidants.

Increased activity of antioxidant enzymes superoxide dismutase (SOD) and catalase in alveolar macrophages from young smokers has been reported [77]. Another spectacular discovery is spin traps, such as  $\alpha$ -phenyl-N-tert-butyl nitron, which directly react with ROS and RNS at the site of inflammation [78]. It has also been reported in animal models that intratracheal instillation of a catalytic antioxidant, manganese(III) mesotetrakis, was able to inhibit cigarette smoke-induced inflammatory response (decreased number of neutrophils and macrophages) [79]. These compounds mimic extracellular SOD and

catalase and are capable of scavenging both lipid peroxides and peroxynitrite.

Ebselen, a seleno-organic compound with enzymatic activity similar to glutathione peroxidase increases the efficiency of the reduced form of glutathione (GSH) as an antioxidant and can thus be used as a therapeutic agent against oxidative stress and inflammation [80, 81]. Molecular engineering of antioxidant genes such as glutathione peroxidase or alteration of genes involved in the synthesis of GSH itself could be a future therapeutic option in genomic medicine.

Dietary polyphenols have antioxidant and anti-inflammatory properties that may explain their beneficial effects [82]. Curcumin, the active principal gradient in turmeric, is used in many ailments, particularly as an anti-inflammatory agent. It has multiple properties to protect against cigarette smoke-mediated oxidative stress [83] and acts as an ROS scavenger, increases antioxidant GSH levels by induction of GCL (gamma-glutamylcysteine ligase), and acts as an anti-inflammatory agent.

## 6. GENETIC RESPONSE TO OXIDATIVE STRESS

The most common biological target for these highly reactive ROS entities is DNA. Evidence shows that continuous oxidative damage of DNA is involved in the pathophysiology of various diseases including COPD. Oxidative stress due to abnormal accumulation of inflammatory cells, including neutrophils and macrophages, and ROS from cigarette smoke can impair vasodilation and endothelial cell growth, followed by modification of proteins, lipids, carbohydrates, and DNA, consequently degrading lung tissue. Although oxidants cannot degrade the extracellular matrix (ECM), they can modify elastins which are highly susceptible to proteolytic cleavage [84]. Thus, there are a cascade of sequences causing lung tissue damage in COPD patients due to excess oxidants, and the interplay of both genetic and environmental factors leading to COPD pathogenesis cannot be ignored. It has been reported that 8-hydroxy-2'-deoxyguanosine (8-OH-dG) expression is significantly increased in the peripheral lung tissues of smokers (with and without COPD) compared with non-smokers, while the number of DNA damage and repair sites were increased in smokers compared with

non-smokers and patients with COPD, implying the existence of a DNA damage/repair imbalance in COPD [85–87].

ROS damage nucleic acids forming oxidative products, requiring multiple repair mechanisms. Moreover given the important role of mitochondria in the DNA damage and the antioxidant capacity in humans, researchers have evaluated the inner mitochondrial membrane proteins (prohibitins, PHB1 and PHB2) in COPD patients and reported that these proteins interact with NADH dehydrogenase protein complex, which is essential for oxidoreductase activity within cells [88]. Smoking, due to increased ROS production, damages the mitochondrial respiratory machinery [89–91]. The oxidative DNA damage in the lung generally affects the base composition of the repeated sequences (microsatellite DNA) especially when coupled with DNA mismatch repair system (MMR) deficiency [86, 92]. The study of MSI in blood samples of COPD patient of Bhopal gas victims offers an index of the estimated DNA disturbance which is achieved with the use of microsatellite markers (CA)<sub>n</sub>RG and (CA)<sub>n</sub>R[Y-Q], targeting specific chromosomal loci near or in genes that could be implicated in the pathogenesis of the disease [93]. The induction of MSI by oxidants in COPD has significant biological relevance, given the association of MSI with chronic inflammation, where oxidant production would be enhanced [94].

## 7. THERAPEUTIC INTERVENTION

COPD is a multi-factorial, irreversible disease with airflow limitation involving chronic bronchitis and emphysema apart from a myriad of systemic manifestations which tend to worsen the disease state. No single mechanism can account for the complex pathology in COPD. It is likely that there exists a synchronization of airway inflammation, protease/anti-protease imbalance, oxidative stress, and apoptosis that worsens conditions in emphysema. However, it is treatable if therapy and patient self management measures of the disease are followed regularly.

Current pharmacotherapy aims at improving symptoms, exercise tolerance, and health status. Patients symptomatic of COPD in the population should be screened and subjected to pharmacological interventions via the use of short-acting bronchodilators to rescue symptoms as a first line of action. However,



when symptoms do not improve, a combination of bronchodilators of different classes is effective. Furthermore, long-acting  $\beta$ -agonists plus inhaled corticosteroids are beneficial [95]. Thiol antioxidants, carbocysteine, erdosteine, and fudosteine are frequently used for increasing lung thiol content. Improvement in cigarette smoke-induced oxidative stress and changes in cellular levels has also been reported to be altered by synthetic molecules, such as spin traps, catalytic antioxidants, porphyrins, and lipid peroxidation and protein carbonylation blockers/inhibitors. Pre-clinical and clinical trials have also shown that these antioxidants can reduce oxidative stress, affect redox and GSH biosynthesis genes, and pro-inflammatory gene expression [96].

The current therapy uses antioxidants for COPD is symptomatic. For example, the thiol-based therapy is mainly mucolytic, thereby minimizing the bacterial/viral load. Additionally, antioxidant compounds may also enhance the efficiency of glucocorticoids by quenching oxidants and aldehydes in COPD patients. Antioxidant therapy may affect important outcomes in COPD, such as overcoming steroid resistance, mucus hypersecretion, inflammation, and extracellular matrix remodeling. Furthermore, the effects of a combination of various antioxidants along with thiols, spin traps, lipid peroxidation/protein carbonylation inhibitors/blockers, or enzyme mimetics is an attractive strategy worth inspecting in patients with COPD. Antioxidants (e.g., thiols and other molecules) may be combined with anti-inflammatories/PDE4 inhibitors/Sirtuin1 activators, bronchodilators, steroids, antibiotics, and statins. Furthermore, new antioxidant strategies can be used as supplementing/pre-emptying agents in the management of COPD, as well as in susceptible smokers [97]. The lung functioning in COPD can deteriorate over time despite receiving the best available care. Antioxidant properties associated with vitamin C (also known as ascorbate or L-ascorbic acid) play significant roles in the immune response including allergic reaction, maintenance of connective tissue, and even tumor suppression. Reduced levels of vitamin C have been associated significantly with elevated wheezing, dyspnea, and exacerbation of COPD. Dietary vitamin C has also been shown to decrease oxidative stress, increase collagen synthesis, and restore vascular endothelial growth factor levels leading to proliferation of alveolar cells in the lungs. Extensive studies have shown that vitamin C intake

provides protection against the development of COPD [98]. In addition to the medical therapies, regular exercise/training and individualized rehabilitation are also of major importance.

## 8. CONCLUSION

COPD continues to progress long after a person quits smoking, as free radicals are partly to be blamed. COPD involves chronic inflammation, and inflammatory cells release abundant free radicals. As a result, the lungs of COPD patients exist in a constant state of oxidative stress—an imbalance of free radicals and antioxidants. Oxidative stress has important implications in several events of lung physiology and in the pathogenesis of COPD. These include oxidative inactivation of antiproteases and surfactants, mucus hypersecretion, membrane lipid peroxidation, dysfunction of mitochondrial respiration, alveolar epithelial injury, remodeling of extracellular matrix, and apoptosis. An increased level of ROS produced in the airways is reflected by increased markers of oxidative stress in the airspaces, sputum, breath, lungs, and blood in patients with COPD. There are several small molecule compounds in clinical trials that target oxidant signalling or quench oxidants derived from cigarette smoke. Antioxidant and/or anti-inflammatory agents such as thiol molecules, spin traps, dietary polyphenols, antioxidant mimetics, and inhibitors of oxidative stress-induced signalling pathways present potential means to treat this element of COPD.

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