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# Role of Reactive Oxygen Species in the Pathogenesis of Bronchial Asthma and Obstructive Pulmonary Diseases: Systematic Review

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**Abstract**

The article discusses the role of reactive oxygen species (ROS) in the pathogenesis of bronchial asthma and obstructive pulmonary diseases. The review follows a structured approach beginning with a comprehensive search of electronic databases, then findings from the included studies were summarized and used to draw comprehensive conclusions. The authors state that increased activity of oxidative processes and insufficient activity of the antioxidant system lead to the accumulation of ROS in the respiratory tract. This leads to direct damage to epithelial cells, activation of inflammatory cells, and stimulation of inflammatory mediators. ROS also activate transcription factors that increase inflammation and airway obstruction. Thus, maintaining the balance of the oxidant-antioxidant system is an important strategy for the treatment of these diseases.

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## Introduction

Respiratory diseases, encompassing a wide range of disorders affecting the lungs and airways, stand as a leading cause of morbidity and mortality globally. Among these, bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD) are particularly significant, affecting a substantial portion of the population across various age groups. The pathogenesis of these diseases involves complex interactions between genetic predispositions, environmental exposures, and lifestyle factors, making their study and management a priority in respiratory medicine. Understanding the underlying mechanisms that drive the onset and progression of BA and COPD is crucial for developing targeted therapies and improving patient outcomes. Moreover, the role of environmental pollutants, occupational exposures, and smoking in exacerbating these conditions highlights the need for a multidisciplinary approach in addressing the public health challenge they pose. As healthcare systems worldwide grapple with the rising costs and the burden of managing chronic respiratory conditions, it becomes imperative to delve deeper into the factors contributing to their pathogenesis.

Bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD) negatively affect the health of millions of people around the world, being the most important factors in increasing healthcare costs [1,2]. The primary cause of hospitalization among pediatric patients experiencing respiratory issues like wheezing, coughing, and breathing difficulties is attributed to BA [1]. COPD stands as a prominent global cause of adult mortality, marked by conditions such as emphysema, bronchitis, and diseases affecting the lower respiratory tract [3]. Individuals with asthma and COPD face a heightened risk of severe exacerbations that could potentially be fatal [2,4].

The most important factors of the etiology and pathogenesis of BA and COPD are, among others, environmental influences that cause oxidative stress (OS), which contributes to damage to the epithelium of the respiratory tract and causes infiltration of their tissues by immunocompetent cells [5-7]. OS strengthening usually causes pathogenesis and an increase in the severity of manifestations of inflammatory lung diseases [8,9].

OS arises from the buildup of RONS and a decline in the functionality of the AOS. RONS play a role in instigating inflammation in the respiratory tract, excessive mucus production, heightened reactivity of the respiratory tract, and structural alterations such as thickening or remodeling, which are distinctive pathological features associated with both BA and COPD [9]. Functional changes in the airways, thickening of their walls, and increased stiffness

contribute to the obstruction of the airways and the development of exacerbations of the diseases in question. Similar structural and functional disorders are even more pronounced in patients with BA and COPD with insensitivity to corticosteroids [10,11]. Individuals afflicted with severe BA or moderate COPD necessitate the use of elevated dosages of corticosteroids, either through inhalation or systemic administration, whereas a decrease in the effectiveness of medications used in normal doses contributes to the development of persistent inflammation of the respiratory tract, their obstruction and an increase in the frequency of exacerbations of the diseases under consideration [12]. It has been found that the expenses of the healthcare system for the treatment of patients with BA and COPD against the background of insensitivity of patients to corticosteroids account for more than 50% of the costs for the therapy of these diseases [13].

The mechanism of reducing sensitivity to corticosteroids under the influence of OS is based on changes in the expression and signaling of the glucocorticoid receptor (GR) [14]. Some studies have shown a connection between the severity of OS and the severity of respiratory tract disease, which confirms the involvement of OS mechanisms in the development of insensitivity to corticosteroids [15].

It seems that OS is a key factor causing pro-inflammatory reactions that contribute to increased inflammation in the tissues of the respiratory tract in the presence of corticosteroids. Inflammation in the respiratory tract is a pivotal factor in the progression of structural and functional alterations that obstruct the airflow and contribute to the onset of exacerbations in both BA) and COPD [14]. The manifestations of inflammation in the respiratory tract are characterized by heterogeneity and certain dynamics, which necessitates the study of the relationship between the progression of lung diseases with various pathophysiological and immunological shifts in the body, which are believed to affect the severity of BA and COPD and the sensitivity of patients to corticosteroids [16,17].

The study aims to provide a systematic review of modern ideas about the participation of reactive oxygen species (ROS) in the development of BA and obstructive pulmonary diseases.

## Methods

### Literature Search and Selection Criteria

This article presents a systematic review to analyze the current understanding of the role of ROS in the pathogenesis of BA and obstructive pulmonary diseases. The review follows a structured approach to identify relevant literature and synthesize the findings.

An extensive literature search was carried out across various electronic databases, notably PubMed, MEDLINE, and Google Scholar. This search aimed to gather pertinent research papers available up to the date of this review. The search terms used included combinations of the following keywords: reactive oxygen species, bronchial asthma, chronic obstructive pulmonary disease, oxidative stress, inflammation, airway obstruction, antioxidant system. Findings from the included studies were summarized and presented in a narrative format. Based on the findings of the systematic review, a comprehensive conclusion was drawn regarding the role of ROS in the pathogenesis of BA and obstructive pulmonary diseases. The implications of the findings were discussed, along with suggestions for further research and potential therapeutic strategies.

## Discussion

### Role of T-lymphocytes in the development of inflammation in the respiratory tract

In allergic BA, the predominant immune response involves the second type of T-helper cells (Th2). This immune profile is commonly observed in both children and adults with mild to moderate asthma [18]. It is characterized by elevated levels of Th2 effector cytokines, specifically interleukins (IL) -4, -5, and -13. These cytokines are produced by CD4<sup>+</sup> Th2 cells and innate immune cells of the second group known as ILC 2. IL-5 primarily contributes to the recruitment of eosinophils, while IL-4 and IL-13 play roles in mucosal cell metaplasia, respiratory hyperreactivity, and airway remodeling [18]. The sensitivity to corticosteroid treatment varies significantly among patients with Th2-type inflammation, with some showing high sensitivity and others having moderate or low sensitivity, particularly in cases of more severe disease.

In contrast, chronic obstructive pulmonary disease (COPD) and severe forms of asthma are frequently characterized by inflammation driven primarily by Th1 and Th17 cells. This type of adaptive immune response stands as a central feature in the pathophysiology of these conditions, distinguishing them from other inflammatory patterns observed in milder forms of respiratory diseases [19,20]. Research has shown that the presence of inflammation associated with Th1 and Th17 responses is linked to a more severe disease course and reduced sensitivity to corticosteroids [19]. The immune responses mediated by Th1 and Th17 cells are marked by their recruitment into the respiratory tract, where they secrete cytokines such as interferon-gamma (IFN- $\gamma$ ) and interleukin-17A (IL-17A). This particular pattern of immune activation is often linked to the body's defense mechanisms against pulmonary infections and injury. The presence of these cells and

their cytokines is a hallmark of the body's effort to repair and protect lung tissue, yet it can also lead to exacerbated inflammatory conditions. The infiltration and activity of Th1 and Th17 cells not only signify the body's response to threats but also contribute to the pathological processes underlying severe respiratory disorders. Their involvement underscores the complex interplay between the immune system and lung health, pointing to the need for therapeutic strategies that can modulate these responses without compromising the body's natural defense mechanisms. Understanding the nuanced role of these T-helper cells in lung pathology could pave the way for innovative treatments aimed at mitigating inflammation while preserving the lungs' ability to fend off infections and heal from damage.

Furthermore, the escalation of inflammation mediated by Th1 and Th17 cells frequently leads to an enhanced presence of neutrophils within the respiratory tract. This phenomenon is closely associated with a diminished response to corticosteroid treatment among individuals suffering from both bronchial asthma and chronic obstructive pulmonary disease (COPD) [21]. IFN- $\gamma$  and IL-17A cause proinflammatory reactions in other immune cells, in the epithelium of the respiratory tract and smooth muscles, neutrophil infiltration of the respiratory tract, and their hyperreactivity and remodeling [22].

The respiratory tract's epithelium consists of a layer of cells lining the inner space of the respiratory tract, serving as a natural barrier that helps prevent pollutants and pathogens from entering the body through inhaled air. In BA and COPD, the integrity of the epithelial barrier of the respiratory tract is disrupted, mucus production increases, and mucus is accumulated, which in turn leads to structural changes and obstruction of the airflow [23].

The inflammatory response within the respiratory tract triggers the secretion of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukin-33 (IL-33), which play a pivotal role in the emergence of Th1 and Th2 mediated inflammation [24]. Corticosteroids inhibit the development of pro-inflammatory reactions in the epithelium of the respiratory tract and ensure the preservation of the integrity of the epithelium when exposed to infectious agents or environmental factors [25]. Therefore, during such therapy of BA or COPD, the formation of mucus in the respiratory tract and the integrity of the epithelium do not significantly change [26].

The persistent thickening and remodeling of the airways, which are distinctive pathological features in both asthma and COPD, play a significant role in obstructing airflow and causing impairments in lung function [27]. The increase in the smooth muscle

component and the activation of fibroblasts in the subepithelial layer of the respiratory tract is explained by increased proliferation and deposition of the extracellular matrix, which eventually leads to hypertrophic changes [28].

Hyperreactivity of the airways is a functional characteristic that determines their tone and the possibility of exacerbations and contributes to the narrowing of the airway lumen in response to the action of bronchoconstrictors, such as histamine [27,29]. Inflammation in the airways enhances the reaction of smooth muscle cells to  $\text{Ca}^{2+}$  ions, and hypercontractility develops, which leads to hyperreactivity of the airways, contributing to disturbances in the function of the respiratory system and increased exacerbations of BA [29].

#### **Factors contributing to OS development**

Reactive Oxygen and Nitrogen Species (RONS) are vital in regulating lung function. When triggered by pro-oxidant and inflammatory environmental factors, they accumulate, leading to cell and tissue damage, and even cell death [30]. Oxidative reactions primarily affect proteins and lipids, causing molecular structure changes and cell function impairments. In Bronchial Asthma (BA) and Chronic Obstructive Pulmonary Disease (COPD), increased RONS levels such as superoxide, hydrogen peroxide, and others are observed in various samples, evidenced by higher oxidative stress markers like malondialdehyde and nitric oxide [30]. In severe asthma and COPD cases, these oxidative stress levels are significantly higher, correlating with worsening patient conditions, symptom severity, and reduced corticosteroid efficacy [31,32].

Changes in the activity of the local immune system of the respiratory tract contribute to an increase in the severity of OS in the lungs. Macrophages, neutrophils, and eosinophils produce RONS in the process of activation during the development of inflammatory reactions [32,33].

Environmental allergens, cigarette smoke, and various pathogens interact with the epithelium of the respiratory tract, which leads to an increase in the levels of exogenous or endogenous RONS, causing the pathogenesis of BA and COPD. In response to increased intracellular oxidative stress, there is a proliferation of cells within the respiratory tract, leading to its thickening. This process is further exacerbated by the activity of eosinophils and neutrophils. These immune cells release enzymes—eosinophilic peroxidase (EPO) and myeloperoxidase (MPO), respectively. These enzymes play a crucial role in the body's response to oxidative stress, contributing to the inflammatory process. This chain of events is significant in the

context of respiratory diseases, as it underscores the complex interplay between immune cell activation, enzyme release, and the structural changes in the respiratory tract, all of which are pivotal in the progression of respiratory conditions. The increased activity of EPO and INR makes an additional contribution to an increase in the severity of OS in the respiratory tract due to the formation of hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) [31-33].

The heightened activity of induced nitric oxide synthase (iNOS) and macrophages significantly influences the generation of Reactive Oxygen and Nitrogen Species (RONS) and the release of inflammatory mediators. Additionally, there's a notable reduction in the efficiency of antioxidant mechanisms like the glutathione system (GS) and superoxide dismutase (SOD) in the epithelial cells of the respiratory tract, particularly in severe cases of Bronchial Asthma (BA) and Chronic Obstructive Pulmonary Disease (COPD). This decrease in antioxidant activity leads to a further escalation in oxidative stress (OS) and inflammation within the respiratory tract.

#### **Environmental factors contributing to OS development** *Allergens*

Both internal and external allergens serve as sources of proteases that can harm the epithelium of the respiratory tract, triggering a significant innate and adaptive immune response [34]. Allergens like house dust mites (HDM), pet dander, pollen, and fungal allergens are pivotal pathogenic factors in BA for both children and adults [35,36]. HDM, for example, can induce Th2-mediated inflammatory reactions, leading to cellular damage and ultimately disruption of the structural and functional integrity of the respiratory tract's epithelial barrier [37]. In cases of BA, sensitization to HDM can result in an escalation of OS severity [35]. The recognition of allergen sensitization as a pivotal element that impacts asthma severity and corticosteroid treatment efficacy is growing. This includes an understanding of how sensitivity to fungal allergens plays a crucial role. Sensitization to various allergens not only exacerbates asthma symptoms but also alters the patient's response to conventional corticosteroid therapies. Such sensitivities underline the need for personalized treatment approaches, emphasizing the importance of identifying specific allergen triggers to manage asthma more effectively and improve therapeutic outcomes [35,38].

#### *Air pollution*

Air quality plays a significant role and is largely influenced by the levels of ozone and particulate matter. Elevated levels of pollutants in the atmosphere contribute to the onset of asthma and COPD [39].

Ozone, as an oxidant, triggers Th17-mediated neutrophilic inflammation in the respiratory tract, which is associated with reduced sensitivity to corticosteroids [40]. Exposure to other environmental pollutants, like diesel engine exhaust fumes and fine particles measuring less than 2.5 microns (PM<sub>2.5</sub>), also leads to the development of severe oxidative stress in the lungs [41,42]. Like ozone, diesel exhaust substances cause inflammation in the lungs of the Th17 type with an increase in IL-17A levels and neutrophil infiltration [43]. Clinical and instrumental methods are crucial in identifying pathogenetic factors behind clinical symptoms and respiratory system disorders. The respiratory health is adversely impacted by prolonged exposure to atmospheric pollution from transport and industrial sources. Such exposure contributes to the deterioration of respiratory health, highlighting the need for thorough clinical and instrumental assessments to understand and address the underlying pathogenetic factors effectively [44].

#### ***Cellular OS mechanisms***

Pulmonary macrophages are an important factor in the development of asthma and COPD. Macrophages present in large numbers in the lungs generate RONS (this reaction is aimed at destroying invading pathogens) [45, 46]. In respiratory bursts, an increase in the activity of iNOS and NADPH oxidase in macrophages leads to an increase in the activity of hydrogen peroxide, nitrogen oxide, superoxides, and peroxynitrite [47].

An increase in the level of RONS in lung macrophages leads to an increase in the production of proinflammatory cytokines [11]. Reactive oxygen and nitrogen species (RONS) adversely affect the capabilities of lung macrophages, reducing their ability to phagocytize pathogens and apoptotic cells – a key process in the pathogenesis of pulmonary diseases [48]. Chronic oxidative stress within these lung macrophages can lead to a decreased responsiveness to corticosteroids in conditions such as severe asthma and chronic obstructive pulmonary disease (COPD) [49].

After infiltration of the lungs and activation during the development and allergic reactions, eosinophils form so-called eosinophil extracellular traps (EVTs) containing EPO and releasing hydrogen peroxide [50]. It has been found that the formation of EVT's and the activity of EPO depend on the formation of RONS and the severity of OS [50]. Interestingly, recent research has shown that hydrogen peroxide can also play a role in promoting eosinophil apoptosis, which is an important mechanism for resolving allergic reactions in patients [51]. Corticosteroids are generally effective in reducing eosinophil levels in the respiratory tract. However, in severe BA, higher doses of these

medications may be required to lower eosinophil counts in both the bloodstream and the lungs [52].

In corticosteroid-resistant patients, there's notable lung infiltration by neutrophils, alongside increased levels of chemoattractants like CXCL1 and CXCL8, indicating a potential insensitivity of neutrophils to corticosteroids in asthma and COPD cases [53]. Furthermore, the persistence of neutrophils in the lungs, possibly due to their prolonged survival [54], exacerbates oxidative stress. This is primarily attributed to the oxidative burst mediated by myeloperoxidase (MPO) [32], contributing significantly to the pathophysiology of these respiratory diseases. Myeloperoxidase (MPO) is involved in producing hydrogen peroxide and forms a part of neutrophil extracellular traps (NETs), which are composed of antimicrobial proteins and enzymes [55]. In severe Bronchial Asthma (BA) patients, neutrophils exhibit increased levels of NETs. This suggests a potential link between elevated NET levels and reduced responsiveness to corticosteroids in these patients [55,56]. The presence and activity of NETs in such conditions indicate a significant role in the pathophysiology of asthma, particularly in the context of corticosteroid resistance.

#### ***AOS of the body***

Cells protect themselves from oxidative stress (OS)-induced damage via a complex array of both enzymatic and non-enzymatic molecules, collectively referred to as antioxidants. These antioxidants operate by ensuring a dynamic equilibrium between the generation and neutralization of reactive oxygen and nitrogen species (RONS), effectively mitigating cellular damage [57]. An imbalance in the oxidant/antioxidant status is associated with bronchial asthma (BA) and the pathogenesis of COPD, contributing to airway obstruction, hyperreactivity, and remodeling. Furthermore, the severity of respiratory tract diseases is directly linked to the amount of RONS generated [58].

In asthma patients, not only is there an increased production of RONS in the lungs, but the levels of antioxidants like SOD and catalase are lower compared to healthy lungs [59]. The reduced activity of the antioxidant system likely plays a role in the reduced responsiveness to corticosteroids [60].

Glutathione (GSH), synthesized intracellularly from amino acids cysteine, glycine, and glutamate, serves as the primary non-enzymatic antioxidant in the lungs [61]. A significant portion, about 90%, of the total lung GSH is in its reduced form. Notably, the epithelial lining fluid in the lungs contains a substantially higher concentration of reduced GSH compared to plasma, with levels reaching around 300 micromoles [61]. This

highlights the critical role of GSH in maintaining lung health and functioning]. Besides its endogenous production, GSH rapidly enters and exits cells, contributing to overcoming OS and the accumulation of oxidized glutathione (GSSG). Therefore, a pool of replenished GSH is crucial to maintaining cell health [61].

In general, both children and adults with BA tend to have lower GSH levels in their serum, lungs, and exhaled air condensate compared to healthy individuals. In a study involving children with BA and adults with COPD, GSH levels in exhaled air were lower in patients compared to healthy subjects, and they increased with oral steroid treatment [61, 62]. Anti-cytokine therapy is a promising approach to the treatment of BA aimed at suppressing the inflammatory process by blocking cytokine signals. Its efficacy and safety require further research and clinical trials [63].

SOD plays a crucial role in catalyzing the conversion of superoxide into hydrogen peroxide. In mammals, there are three isoforms of this enzyme [2]. Copper and zinc-associated SOD accounts for approximately 80-90% of the enzyme's intracellular activity and is primarily found in the cytosol. About 10% of intracellular SOD activity is attributed to the manganese-associated form. This form initially resides in the cytosol but is later transported to the mitochondria, mainly located in the mitochondrial matrix. Extracellular SOD (EC-SOD) is a secreted form of the enzyme found in the lung interstitial space, particularly around blood vessels and the respiratory tract.

Superoxide dismutase (SOD) is a vital enzyme found in all mammalian cells, including in the mucous membrane fluids and epithelial cells of the lungs, particularly in patients with BA and COPD. In these patients, SOD shows lower levels of expression and activity compared to healthy individuals. The reduction in SOD activity, which can occur rapidly, is often linked to protein modifications that impair its enzymatic functionality. Specifically, CuZn-SOD is inactivated by the oxidation of critical histidine residues, while Mn-SOD is inactivated by chlorination and nitration of tyrosine residues, respectively. These modifications contribute to an increase in RONS, exacerbating OS, and ultimately leading to increased hyperreactivity and remodeling of the respiratory tract during an asthma exacerbation.

Catalase, an oxidoreductase enzyme, plays a crucial role in neutralizing hydrogen peroxide alongside other antioxidants. Its effectiveness is notable at high concentrations. However, in conditions of sustained oxidative stress, such as those observed in bronchial asthma, there is a notable reduction in catalase

activity. This reduction stems from the modification of tyrosine residues within the enzyme. This phenomenon has been particularly observed in the lungs of patients suffering from bronchial asthma, indicating a compromised antioxidant defense in such conditions. While catalase plays a pivotal role in neutralizing hydrogen peroxide and is often seen as a frontline defense in oxidative stress (OS), its effectiveness can be significantly compromised during chronic OS conditions. The diminishment of this crucial protective process leads to ongoing inflammation within the respiratory system and fosters resistance to corticosteroid treatments. Such a scenario underscores the challenges in managing chronic respiratory conditions, highlighting the need for therapeutic strategies that can restore or enhance the antioxidant capacity, including catalase function, to mitigate inflammation and improve corticosteroid sensitivity.

#### ***Nuclear factor associated with erythroid 2 (Nrf2)***

Nrf2 is a transcription factor responsible for orchestrating the expression of genes that are involved in protecting cells from OS and damage [64]. In the cytosol, Nrf2 binds to Keap1, a protein that acts as a regulator. When exposed to conditions of OS, Nrf2 is released from Keap1, allowing it to translocate to the cell nucleus. Once in the nucleus, Nrf2 binds to specific elements associated with the antioxidant response, ultimately leading to the activation of genes responsible for the endogenous antioxidant response [65].

Nrf2 directly regulates the expression of over 500 genes, including some involved in the GSH system. The antioxidant activity governed by Nrf2 is crucial for maintaining the balance of the lung's internal environment in the face of oxidative injuries, which plays a pivotal role in limiting pro-inflammatory reactions [64]. It has been found that infection of mice with Nrf2 allergen knockout leads to severe inflammation of the respiratory tract, which is manifested by an increase in leukocyte infiltration and cytokine levels [65].

In severe instances of asthma and chronic obstructive pulmonary disease (COPD), a significant reduction in the expression and functional activity of Nuclear factor erythroid 2-related factor 2 (Nrf2) is observed. This decline contributes to an increase in oxidative stress (OS) and inflammation within the respiratory system [66, 67]. Studies have demonstrated that changes in the levels of Nrf2, along with modifications after the protein is made, are linked to decreased activity of this critical antioxidant pathway in children suffering from severe forms of asthma. Such reductions in Nrf2 functionality exacerbate the oxidative burden, underscoring the vital role Nrf2 plays in maintaining

cellular defense against oxidative damage [36]. This insight into Nrf2's diminished role in severe respiratory conditions highlights the potential for targeted therapies aimed at enhancing Nrf2 activation as a novel approach to mitigating the adverse effects of oxidative stress and inflammation in patients with severe asthma and COPD.

Furthermore, the levels of Nrf2 protein and Nrf2-mediated antioxidant responses are diminished in the smooth muscle cells of the respiratory tract in patients with BA compared to healthy individuals. It is believed that the mechanism regulated by Nrf2 also plays a significant role in the development of airway hyperreactivity and remodeling. Considering Nrf2's pivotal role in mediating lung inflammation and orchestrating the regulation of intrinsic antioxidant mechanisms, it is identified as a promising therapeutic target for the management of asthma and chronic obstructive pulmonary disease (COPD). This perspective is grounded in the understanding of Nrf2's integral function in cellular defense against oxidative stress, suggesting potential for innovative treatment strategies that leverage its regulatory capacity to ameliorate respiratory disorders.

## Conclusion

OS is the most important factor in respiratory tract inflammation and contributes to insensitivity to corticosteroids in patients with obstructive pulmonary diseases. The optimal effectiveness of corticosteroids may depend on maintaining a low level of OS. This highlights the need to develop and improve strategies that contribute to maintaining a homeostatic redox balance in patients with BA and COPD, including in patients receiving corticosteroids.

Currently, some researchers believe that the development of treatment methods aimed at reducing the severity of OS has therapeutic prospects, but further research is needed to clarify the mechanisms for the implementation of manifestations of OS in the respiratory tract.

In light of these considerations, future research directions should emphasize the identification and development of novel therapeutic agents that can effectively reduce oxidative stress within the respiratory system. Such interventions could potentially enhance the responsiveness to corticosteroids and offer a more personalized approach to managing obstructive pulmonary diseases. Moreover, integrating antioxidant therapies with current treatment regimens may offer a synergistic effect, further stabilizing the redox balance and mitigating inflammation in the respiratory tract. It is imperative that upcoming studies also focus on the long-term effects of these interventions to ensure that

they do not only offer temporary relief but also contribute to a sustained improvement in the quality of life for patients with BA and COPD. This holistic approach to treatment underscores the complexity of obstructive pulmonary diseases and the multifaceted strategies required to address them effectively.

## Author Contributions

Imetkul D. Ismailov: Wrote the final paper, participated in research and editing of the article.

Romanbek K. Kalmatov: Drafted, participated in writing and research for the article, aided in data collection and editing of the manuscript.

Baktyiar O. Abdurakhmanov: Participated in all stages of the research and writing, Is responsible for graphic design, participated in research and editing of the article.

Ali Munir Mirza: Participated in writing and editing the final version of the manuscript, aided with all the paperwork and drafting.

Jitendra Kumar Chaurasia: Was responsible was data collection and data management, aided with editing and cleaning up the manuscript.

## Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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