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**Advance of antioxidants in asthma treatment**

Zhu LY *et al*. Antioxidants in asthma

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**Abstract**

Asthma is an allergic disease, characterized as a recurrent airflow limitation, airway hyperreactivity, and chronic inflammation, involving a variety of cells and cytokines. Reactive oxygen species have been proven to play an important role in asthma. The pathogenesis of oxidative stress in asthma involves an imbalance between oxidant and antioxidant systems that is caused by environment pollutants or endogenous reactive oxygen species from inflammation cells. There is growing evidence that antioxidant treatments that include vitamins and food supplements have been shown to ameliorate this oxidative stress while improving the symptoms and decreasing the severity of asthma. In this review, we summarize recent studies that are related to the mechanisms and biomarkers of oxidative stress, antioxidant treatments in asthma.

**Key words:** Asthma; Oxidative stress; Reactive oxygen species; Antioxidants

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**Core tip:** Oxidative stress plays important role in the pathogenesis of asthma. The imbalance of oxidative and anti-oxidative system is caused by exogenous and endogenous reactive oxygen species. Some elevated substances could be served as oxidative or antioxidative biomarkers. Different kinds of treatments showed antioxidative role, including diet, vitamins and food supplements; natural extracts; magnetic field and laser, *etc*. However, no antioxidants were applied in first-line therapy of asthma now. More works are needed, especially clinical trial, to clarify the clinical value of antioxidant therapy.

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Asthma is a chronic inflammatory lung disease that is induced by cellular mechanisms that result in airway hyper-reactivity and airflow limitation[[1](#_ENREF_1)]. Patients with asthma suffer from a variety of symptoms, including dyspnea, recurrent coughing, chest tightness, shortness of breath and sporadic, frequent wheezing[[2](#_ENREF_2)]. Previous studies have indicated that oxidative stress plays an important role in the development of asthma[[3](#_ENREF_3)]. Reactive oxygen species (ROS) present in asthmatic airways are derived from many sources, including exposure to environmental peroxidants, infiltration of inflammatory cells in the airway, metabolic disorders, and decreased levels of cellular antioxidants. Airway oxidative stress also has been associated with declining disease status, poor lung function, and epigenetic changes[[4](#_ENREF_4)].

Antioxidative treatment, such as food supplements[[5](#_ENREF_5),[6](#_ENREF_6)] and vitamins[[7](#_ENREF_7)], is a potential therapy for asthma, but has not been denoted as a first-line method because current results are not consistent with clinical data. In this review, we have summarized the recent literature related to oxidative stress characteristics and antioxidants treatments in asthma.

**OXIDATIVE STRESS RESPONSE IN ASTHMA**

***Sources of ROS and asthma***

**Exposure to exogenous ROS and asthma:** Airway epithelial cells are in close contact with the external environment in humans. When asthmatic patients are exposed to exogenous ROS-such as environmental tobacco smoke[[8](#_ENREF_8)], airborne pollution[[9](#_ENREF_9)], home dust mites[[10](#_ENREF_10)] or sulfar mustard[[11](#_ENREF_11)]-in the air, which may trigger symptoms of asthma.

Outdoor air pollution is definitely associated with the incidence of asthma[[12](#_ENREF_12)]. As primary air pollutants, exposure to O3 or NO2 can cause inflammation and repair, as indicated by secretion of chemokines and cytokines[[13](#_ENREF_13),[14](#_ENREF_14)]. O3 exposure may increase the NK-1R gene expression and then induce subsequent acute oxidant stress[[15](#_ENREF_15)]. Inhalation of Cl2 results in oxidative lung injury by ROS and low-molecular-weight hyaluronan, which then activates the RhoA and Ca2+ channels of airway smooth muscle cells, resulting in airway hyper-responsiveness (AHR)[[16](#_ENREF_16)]. Particulate matter (PM), a major component of air pollution, includes diesel soot, welding fumes, carbon black, coal or oil fly ash. Diesel exhaust inhalation may increase airway responsiveness[[17](#_ENREF_17)], decrease total cysteine levels, increase cystine and s-glutathionylated cysteine in bronchoalveolar lavage fluid(BALF)[[18](#_ENREF_18)], increase nitrite and decrease pH in exhaled breath condensate (EBC)[[19](#_ENREF_19),[20](#_ENREF_20)]. Further studies have demonstrated that an assay of oxidative potential was more closely associated with lung function than PM2.5 mass by measuring dithiothreitol levels[[21](#_ENREF_21)]. Cigarette smoking is also a high risk factor for asthma. Passive smoking could impair histone deacytylase-2 function *via* PI3K signaling activation, which reduces histone deacetylase-2 protein expression[[8](#_ENREF_8)]. Cigarette exposure can induce the expression of GPx-1 (glutathione peroxidase-1)-PYP1B (protein tyrosine phosphatase-1B)-PP2A (protein phosphatase-2A), which may induce the destruction of lung tissue[[22](#_ENREF_22)].

Indoor pollution cannot be ignored. Dermatophagoides species produce O2- by converting the dehydrogenase form of XOR to the oxidase form[[10](#_ENREF_10)], which may be associated with increased levels of DNA repair proteins and apoptosis[[23](#_ENREF_23)]. Hexabromocyclododecane and phthalates are indoor pollutants that may enhance inflammatory cytokines expression[[24](#_ENREF_24),[25](#_ENREF_25)]. Urinary 2-phenanthrene, 1-pyrene and Di- (2-ethylhexyl) phthalate have been found to be associated with asthma diagnoses[[26](#_ENREF_26),[27](#_ENREF_27)]. Observations in cleaning workers have revealed decreases in non-reversible lung function and a total increase in IgE levels[[28](#_ENREF_28)]. These chemicals and acrolein induce the production of ROS and malodialdehyde while decreasing glutathione (GSH) levels[[24](#_ENREF_24),[25](#_ENREF_25),[27](#_ENREF_27),[29](#_ENREF_29)].

**Endogenous ROS and asthma:** Endogenous ROS is associated with enzymes produced by inflammatory or epithelial cells, which is induced by inflammation during the immune response to pathogens or allergenic substances. The main source of intracellular ROS is from mitochondrial respiration, produced primarily by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, as well as the xanthine/xanthine oxidase system. O2- is produced by these enzymes in activated cells, such as eosinophils or macrophages, and O2- also can generate ONOO- from either NO or by transfer onto H2O2 *via* superoxide dismutase (SOD). H2O2 may cause the generation of the more oxidative OH- by the Fenton reaction when Fe2+ is present[[30](#_ENREF_30)]. Macrophages produce ROS *via* other enzymes, such as heme peroxidase, myeloperoxidase (MPO) or eosinophilic peroxidase (EPO). Hypochlorous acid and hypobromous acid can be generated by these enzyme-mediated chain reaction in the presence of Cl- or Br-, which are more oxidative and toxic[[31](#_ENREF_31)].

The formation of hypohalite and hypobromite results in increasing NO levels, which is produced by epithelial inducible nitric oxide synthase (iNOS). Reactive nitrogen species (RNS) then may quickly be formed in the presence of ROS[[32](#_ENREF_32)]. High levels of protein nitration, such as bromotyrosine adducts, have been observed in inflammatory airways and are associated with low control of asthma[[33](#_ENREF_33)].

***The role of oxidative stress and defense mechanisms in asthma***

Increases in ROS levels are strongly related to the severity of asthma in patients[[34](#_ENREF_34)]. There are higher amounts of ROS and RNS in asthmatic patients, which leads to airway inflammation[[35](#_ENREF_35)]. ROS/RNS activate nuclear factor-κB (NF-κB), mitogen-activated protein kinase (MAPK), activator protein -1, and other transcription factors, which result in lung inflammation[[35-39](#_ENREF_35)]. These redox-sensitive transcription factors promote the expression of many proinflammatory cytokines-such as interleukin (IL) -6, IL-8, and tumor necrosis factor alpha (TNF–α)-which then induce activation of inflammatory cells in the airways[[40](#_ENREF_40),[41](#_ENREF_41)], further leading to lung tissue damage and destruction[[22](#_ENREF_22)]. CysLTrl(-/-) mice had abnormal antioxidant response and increased susceptibility to oxidative damage[[42](#_ENREF_42)]. Deficiency in mannose-binding lectin could notably diminish pulmonary inflammation after exposure to O3[[43](#_ENREF_43)].

Nuclear factor erythroid 2-related factor 2 (Nrf2) is an NF-E2-related factor of exogenous toxins and oxidative stresses that plays an important role in oxidative stress defense mechanisms[[44](#_ENREF_44)]. As a vital factor in the antioxidant pathway, Nrf2 activates antioxidant enzymes that catalyze ROS into non-toxic substances and that are water soluble, which is conducive to balancing the oxidative and antioxidative system in the body[[45](#_ENREF_45)]. Nrf2-deficient mice had elevated levels of oxidative stress, inflammation, mucus, and AHR, which resulted in a higher incidence of asthma[[40](#_ENREF_40)].

**Biomarkers of oxidative stress in asthma:** As mentioned previously, O2- and NO are mainly produced by NADPH oxidase and iNOS, respectively, while O2- is dismutated to form H2O2. These oxidative species are all found at high levels in the EBC of asthmatic patients[[46](#_ENREF_46)]. Some parameters that are indirect measurements of ROS-including carbonys, nitrotyrosine, isoprostanes, and 8-hydroxydeoxyguanosine-can provide important information regarding the overall oxidant load. Oxidative stress lipid peroxides are end products formed during ROS-mediated attacks on cell membranes, and these include pentane, ethane, isoprostanes, MDA, and thiobarbituric acid reactive substances (TBARS). 8-isoprostanes are novel biomarkers that can be used to evaluate oxidative stress, and are significantly elevated in the sputum, EBC, plasma, and lung tissues of asthma objects[[47-50](#_ENREF_47)]. However, concentration of 8-isoprostanes in EBC did not increase after bronchial provocation or were not altered between asthmatic and healthy patients[[51](#_ENREF_51),[52](#_ENREF_52)]. Asthmatic patients had increased levels of MDA in their plasma, EBC, and sputum[[53-58](#_ENREF_53)]. Higher blood levels of TBARS were found in asthmatic children[[59](#_ENREF_59)]. DNA can be attacked by ROS, and 8-oxo-deoxyguanosine is a biomarker for DNA damage. NADPH oxidase-4 is overexpressed in asthmatic patients and the level of 8-oxo-deoxyguanosine was more highly elevated in patients with neutrophilic asthma than those with non-neutrophilic asthma[[60](#_ENREF_60)]. Amino acid oxidation of the protein backbone occurred by ROS *via* a MPO/EPO catalyzed reaction with halide ions or nitrite on tyrosine, causing nitrotyrosine, bromotyroxine, chlorotyrosine, and carbonyl modifications. For example, 3-nitrotyrosine was found to have a negative correlation with percentage predicted forced expiratory volume in one second (FEV1 % pred)[[54](#_ENREF_54)], and levels of 3-nitrotyrosine in maternal blood and cord blood were notably elevated in allergic asthma[[61](#_ENREF_61)]. Total oxidant status (TOS) was used as a direct parameters to evaluate whole body oxidative status, and this was significantly higher in asthma patients[[62](#_ENREF_62)].

**Oxidative stress and airway inflammation in asthma:** Oxidative stress has been implicated in the pathogenesis of asthma. Endogenous H2O2 may increase the activity of matrix metalloproteinase-9, an important inflammation biomarker. In asthmatic patients, matrix metalloproteinase-9 activity and 8-isoprostane levels were significantly increased under acute exacerbation and were decreased in remission, but were still higher than in healthy controls relative to the plasma levels of total matrix metalloproteinase-9[[48](#_ENREF_48)]. TNF-α levels were increased in the plasma and lung tissues of both ovalbumin (OVA)-sensitized guinea pigs and obese mice[[63](#_ENREF_63),[64](#_ENREF_64)]. TNF-α may induce mitochondria to generate endogenous ROS[[65](#_ENREF_65)]. Th2-cytokine response (like IL-4 or IL-5) was observed to be higher in asthma exacerbations, whereas O3 could notably induce IL-6, IL-8 expression[[13](#_ENREF_13),[66](#_ENREF_66)]. After H2O2 inhalation, Th17-related proinflammatory markers were upregulated in both liver and vasculature, and this result suggested that ROS inhalation may cause systemic inflammation[[67](#_ENREF_67)].

ROS are related to airway inflammation in asthma. Cell signals are activated by DNA repair-mediated oxidation, which results in gene expression from epithelial and submucosal tissues, leading to smooth muscle contractions of the airway[[68](#_ENREF_68)]. Lim *et al*[[69](#_ENREF_69)] discovered that pulmonary eosinophilia, AHR, mucus hypersecretion and iNOS were significantly elevated in OVA-induced asthma mice. This phenomenon could be suppressed using SRS27, an NF-κB inhibitor. H2O2 may reduce epithelial resistance, induce epithelial damage and decrease epithelial responsiveness and suppress the anti-inflammation role of corticosteroids[[70](#_ENREF_70)]. Changes in the ultramicrostructure and reduction of mitochondrial respiratory membrane protein complex protein in airway epithelial cells are associated with the recruitment of inflammatory cells caused by an oxidizing environment. Allergens may exacerbate eosinophil infiltration in airway epithelial cells, cause mitochondrial dysfunction and affect the balance between Th1 and Th2 cell immune response[[71](#_ENREF_71)]. Aquarporin-3(-/-) mice were reduced in airway inflammation after decreasing chemokine (C-C motif) ligand (CCL)24 and CCL22 levels *via* reduced levels of cellular H2O2[[72](#_ENREF_72)].

**Biomarkers of antioxidation in asthma:** With respect to TOS, total antioxidant status (TAS) or total antioxidant capacity (TAC) are used to assess overall non-enzymatic antioxidant potential. Some studies have demonstrated that TAS or TAC was notably higher in asthma than in healthy controls[[55](#_ENREF_55),[62](#_ENREF_62)], although several studies have reported conflicting results. Fatani et al. observed that TAC levels were significantly decreased in emergency asthmatic patients in contrast to outpatient[[53](#_ENREF_53)]. In asthmatic children, TAC was found to be lower in recurrent wheezing children than healthy children, and the numbers of wheezing episodes in the last 6 mo were negatively correlated with serum TAC, hair Zn, and Se levels[[73](#_ENREF_73)]. Yoon *et al*[[74](#_ENREF_74)] observed that serum TAC levels were positively correlated to forced expiratory volume in 1 second (FEV1) at baseline. After adjusting for related factors, the results were not significantly different after a sufficient observation duration.

Enzymatic antioxidants-such as SODs, catalase, and GPxs-may reduce ROS and hydroperoxides to less harmful and water-soluble products. SOD activities were decreased in asthmatic patients, while CuZnSOD activity was also found to be significantly lower in asthma patients when compared to healthy controls[[55](#_ENREF_55),[75](#_ENREF_75),[76](#_ENREF_76)]. Serum level and activity of GPx was remarkably lower in asthmatic individuals[[77](#_ENREF_77),[78](#_ENREF_78)]. Paraoxonase 1 (PON1) is an esterase enzyme that displays antioxidant characteristics. The PON1 activity in the asthmatic patients was significantly lower compared to healthy controls. Interestingly, PON1 presented an area under roc curve of 0.679 for the identification of uncontrolled asthma[[62](#_ENREF_62),[79](#_ENREF_79)].

Non-enzymatic antioxidants include glutathione proteins, sulfhydryls, and vitamin C. There were remarkably lower levels of total thiols, protein sulfhydryls, ascorbic acid and NO in asthma patients[[53](#_ENREF_53),[55](#_ENREF_55),[75](#_ENREF_75),[77](#_ENREF_77)]. As a novel inflammation-associated biomarker, clusterin is a sensitive cellular biosensor of oxidative stress. Hong *et al*[[80](#_ENREF_80)] discovered that CCL20 secretion was negatively associated with clusterin expression in EBC, while clusterin also reduced intracellular ROS levels. Expression of clusterin in the sputum of asthmatic children was higher than in healthy children, and clusterin was more elevated in eosinophil-dominant sputum than in non-eosinophilic sputum. Furthermore, clusterin levels were associated with asthma severity, but these levels were lower when asthma was exacerbated[[81](#_ENREF_81),[82](#_ENREF_82)].

***Genetic association and oxidative stress in asthma***

Gene polymorphisms can be involved in the oxidative stress response. Glutathione S-transferase (GST) is a key enzyme that acts in the initial step of binding in glutathione-catalyzed reactions, which occurs primarily in the cytosol. GST genes control π-class GST activity. Further work has revealed that the genotype of Ile105Val and the allele frequency of Val105 in GSTP1 were higher than in healthy controls, and these features are linked to the severity of airway dysfunction and airway hyper-reactivity[[83](#_ENREF_83),[84](#_ENREF_84)]. The risk of asthma diagnosis is increased when GSTP1 with an AA genotype is accompanied by supplementation with low intake of vitamin A[[85](#_ENREF_85)]. Mice that were null for GSTT1 had an associated increased amount of recurrent wheezing and risk of asthma[[86](#_ENREF_86),[87](#_ENREF_87)]. Lower threshold concentrations of allergen could produce bronchoconstriction in GSTM1 wild-type asthma but GSTM1 wild-type asthma was not associated with risk of asthma[[87](#_ENREF_87),[88](#_ENREF_88)]. GSTA1 (C/T) and *GSTO2* genes were found to be related to allergies and risk factors for asthma[[89](#_ENREF_89)]. The RR genotype of PON1 gene gave a higher risk of asthma, whereas the TT genotype of the catalase gene and T allele of resistance-1 gene more frequently appeared in asthma patients[[79](#_ENREF_79),[90](#_ENREF_90),[91](#_ENREF_91)].

**ANTIOXIDATIVE TREATMENTS IN ASTHMA**

Based on the oxidative stress reaction and defense mechanism, the following antioxidant therapies may be effective in asthma.

***Diet, vitamins and food supplements***

Foods and nutrients could be utilized to protect airways and lung tissue from oxidative damage through a variety of mechanisms. Vitamin E, a fat-soluble vitamin, is a major defense against ROS, which is the primary source of oxidant-induced membrane damage in the human body. Vitamin C, a water soluble vitamin, is responsible for maintaining the antioxidant capacity in the aqueous phase, while also contributing to the membrane-bound oxidative regeneration of vitamin E. Similarly, vitamin A and vitamin A carotenoids-such as α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, and lycopene-have antioxidant properties. Selenium is incorporated into the antioxidant enzyme GPx, which reduces the organic peroxide H2O2, thereby preventing peroxidation of cell membrane lipids and subsequent instability. Zinc is present in all cells and is an essential trace element in thousands of catalytic proteins and transcription factors, and this metal can be used as an antioxidant. All of these vitamins and nutrients can be found in fruits, vegetables, seeds, seafood, seed oils, nuts and beef[[92](#_ENREF_92),[93](#_ENREF_93)]. Asthmatic adults with low-antioxidant diets have lower FEV1 scores, lower percentage predicted forced vital capacity, higher plasma C-reactive protein and more frequent exacerbation than those on a high-antioxidant diet[[94](#_ENREF_94)], whereas supplementation notably improved both symptoms and lung function in exercise-induced asthma[[95](#_ENREF_95)]. Vitamin A, Vitamin E, and Se were found significantly lower in asthma than in controls, and Vitamin E was negatively impacted by FeNO and MDA. FeNO level was significantly decreased during a study involving nutraceutical supplements[[5](#_ENREF_5),[54](#_ENREF_54)]. The Vitamin E isoform γ-Tocotrienol increased the level of Nrf2 by blocking NF-κB, and inhibited oxidative damage by promoting endogenous antioxidant production in the lung[[96](#_ENREF_96)]. More important, γ-Tocotrienol improved acetylcholine- or methacholine-induced AHR, while also reducing lipopolysaccharides (LPS)-induced neutrophil infiltration[[96-98](#_ENREF_96)]. In contrast, food supplements did not upregulate glutathione or oxidized glutathione and were irrelevant to the incidence of asthma[[99](#_ENREF_99),[100](#_ENREF_100)].

Vitamin D is from dietary intake or synthesized in the skin during exposure to UVB. Severe asthma patients that were deficient in Vitamin D had lower FEV1 values compared to patients with sufficient Vitamin D during exacerbation. The absence of Vitamin D3 could enhance ROS and DNA damage *via* TNF-α release and NF-κB expression. Vitamin D3 supplementation was able to reverse this phenomenon[[7](#_ENREF_7)]. Treatment with vitamin D3 reduced OVA-induced airway inflammation, immunoglobulin E overexpression, expression of α-smooth muscle actin, collagen deposition, and goblet cell hyperplasia, but does enhance activation of the Nrf2/HO-1 pathway[[101](#_ENREF_101)].

Cockroach extract-immunized mice significantly increased AHR. Combined supplementation with choline chloride, vitamin C, and selenium could potentially reduce AHR, inflammation and oxidative stress by inducing IL-10 expression *via* FOXP3(+) signaling[[102](#_ENREF_102)]. A comparison between organic selenium (Pro-Se) and inorganic selenium has implicated that Pro-Se might significantly elevate serum SE levels and restore endogenous antioxidant enzyme levels. Furthermore, Pro-Se does not accumulate in liver and kidney and, thus, has lower toxicity[[103](#_ENREF_103)]. Resolvin-D1 inhibited H2O2 and IL-8 both in mRNA and protein level in 16 human bronchial epithelial cells stimulated by cigarette smoke extract through degradation and NF-κB activation[[104](#_ENREF_104)].

***Thiol antioxidants***

In antioxidant therapy, thiol antioxidants are popular supplements to cause glutathione conversion. N-acetyl cysteine (NAC) is the most commonly used thiol precursor. Challenge with OVA increases airway inflammation and vascular inflammation, while treatment with NAC significantly inhibits ROS and lipid peroxides[[105](#_ENREF_105)]. NAC supplementation reduces baseline airway responsiveness when irritated by diesel exhaust inhalation and also reduces use of bronchodilators[[17](#_ENREF_17)]. In mice BALF, NAC application remarkably decreases inflammatory cytokines (IL-13, IL-5), neutrophil and eosinophil numbers[[106](#_ENREF_106)].

***Natural extracts***

Natural extracts contain antioxidant compounds derived from plants, such as benzoic acid, cinnamic acid, coumarin, gallnut tannic acid, and flavonoids. Sakuranetin is a flavonoid and treatment with sakuranetin can attenuate AHR, while decreasing 8-isoprostane, Th2 pro-inflammatory cytokines, IgE, and vascular endothelial growth factor levels, as well as remodeling airways by inhibiting NF-κB activation[[107](#_ENREF_107),[108](#_ENREF_108)]. Astragalin, another flavonoid, suppresses eosinaphilia infiltration stimulated by LPS and H2O2 via the Toll-like receptor 4-PKCβ-NADPH signaling pathway[[109](#_ENREF_109)].

Resveratrol is a polyphenolic compound that is mainly found in peanuts, grapes (red wine), *Polygonum cuspidatum*, mulberry, and other plants and is a strong natural biological polyphenol. OVA-challenged obese mice had more eosinophil infiltration in lung tissue than in lean mice, and resveratrol decreases p47phox expression and ROS production, increases SOD levels and reverses elevated TNF-α and iNOS in the lung tissues[[63](#_ENREF_63)]. Resveratrol treatment in allergic mice decreases oxidative stress and significantly restores mitochondrial function. In asthma, resveratrol probably downregulates the phosphoinositide 3-kinase-protein kinase B pathway by upregulating inositol polyphosphate 4 phosphatase[[110](#_ENREF_110)].

Morin, an active ingredient obtained from Moracease plants, which attenuates the extensive trafficking of inflammatory cells into BALF in OVA-challenged mice, inhibiting the inflammation infiltration into lung tissue. Morin abolished intracellular ROS and MAPK[[111](#_ENREF_111)]. Ethyl acetate fraction from Sonchus asper extract, Boerhavia procumbens in toluene diisocyanate and Esculentoside A inhibited oxidative stress pathways, reducing anti-inflammatory response and improving lung injury[[112](#_ENREF_112)]. Ethyl acetate fraction and Esculentoside A treatment significantly upregulated Nrf-2 expression, increased SOD activity and intracellular glutathione levels[[113](#_ENREF_113),[114](#_ENREF_114)]. Oral treatment with Capsicum annuum L. methanolic extract remarkably decreased the pathophysiological signs of allergic airway disease, reducing ROS levels of BALF in mice and inhibiting Th-2 cytokines via attenuated NF-κB activation[[115](#_ENREF_115)].

In addition to maintaining the balance between oxidative and antioxidative systems in lung tissues and airways, these substances also suppress mucous gland hypertrophy, goblet cell hyperplasia, collagen deposition and airway remodeling, including the extracts of Sinomenine, Morin, Tinospora cordifolia and Gleditsia sinesis[[111](#_ENREF_111),[116-118](#_ENREF_116)].

LPS is commonly found in the environment, causing and potentially exacerbating airway inflammation, which leads to an increase in IgE levels, Th2-cytokines response, histamine release, and EPO and MPO activation. Intranasal curcumin could significantly improve asthma exacerbation induced by LPS[[66](#_ENREF_66)]. Carissa opaca fruit extracts can restore the activities of antioxidant enzymes and GSH, while the amount of TBARS and DNA fragmentation also decreased[[119](#_ENREF_119)]. Such phenomenon was partly observed when using tomato juice treatment[[120](#_ENREF_120)].

***Antioxidant synthetics***

Y-27632, a Rho-kinase inhibitor, is able to control airway inflammation, airway responsiveness, remodeling and oxidative stress. Y-27632 treatment in guinea pigs induced by allergens provoked decreased FeNO levels, while inflammation, extracellular matrix remodeling, and oxidative stress in the lung were also attenuated[[121](#_ENREF_121),[122](#_ENREF_122)].

Nitric oxide synthases (NOS), H2S and arginases are thought to be involved in lung allergy disease. Treatment with 1400W (an iNOS-specific inhibitor), nor-HOHA (an arginase inhibitor) or NaHS (a H2S donor sodium hydrosulfide) reduces the expression of arginase 2, 8-isoprostane and NF-κB in distal lung tissue. These inhibitors also decreased eosinophil infiltration in lung tissues, subsequently improving tissue resistance and elastance[[49](#_ENREF_49),[123](#_ENREF_123)].

Some compounds could act on ROS signaling pathways directly and indirectly to cause antioxidant effects. HYDAMTIQ is a new poly (ADP-ribose) polymerase inhibitor that prevents airway damage in asthma. Treatment with HYDAMTIQ reduces MDA, 8-hydroxy-2’-deoxyguanosine, the amount of eosinophils and other leucocytes in lung tissue, while also reducing smooth muscle and globlet cell hyperplasia, whereas the mast cells of HYDAMTIQ-treated animals have reduced histamine release in vitro when exposed to OVA[[124](#_ENREF_124)]. Phosphorylation of histone 3 at serine 10 is related to oxidant-associated inflammation. P38α MAPK and IκB kinase 2 signaling pathway may be affected by ROS, as the combined usage of p38α MAPK and IκB kinase 2 inhibitors, reduced histone 3 at serine 10, inflammatory gene expression in monocytes and lung macrophages from asthmatic patients[[36](#_ENREF_36)]. Angiotensin-I converting enzyme 2 (ACE2) is an enzyme that protects against asthma. An ACE2 activator, diminazene aceturate, prevents asthmatic lung that is induced by cytokine expression and elevated levels of ACE2 and IκB. Diminazene aceturate could also decrease carbachol (as an oxidative parameter), attenuate oxidative stress, reverse airway remodeling and right ventricular hypertrophy[[125](#_ENREF_125)]. Diallyl sulfide decreases infiltrated inflammatory cell counts and Th2 proinflammatory cytokines in BALF in OVA-induced mice *via* Nrf2 activation by regulating microRNA-144, -34a, and -34b/c[[126](#_ENREF_126)].

Mice treated with S-adenosylmethionine, a potent methyl donor, had decreased amounts of Th-2 proinflammatory cytokines and 4-hydroxy-2-nonenal in lung tissues, while airway inflammation and fibrosis is suppressed by in mice[[127](#_ENREF_127)]. Pituitary adenylate cyclase-activating polypeptide reverses vanadate-induced AHR, principally through bronchodilator activity and counteraction of proinflammatory and prooxidative effects[[128](#_ENREF_128)].

***Metals and new materials***

Tiron treated mice could significantly attenuate OVA-induced oxidative stress, by reducing pulmonary MDA and increasing GSH and SOD levels. Tiron could also minimize immunoreactivity of NF-κB in these mice, and down regulate levels of NOx, IL-13 and TGF-β1[[129](#_ENREF_129)].

Nanoparticles are proved to be antioxidative objects. Gold nanoparticles treated mice, the levels of pro-inflammatory cytokines and ROS were inhibited, mucus production, peribronchiolar fibrosis and AHR induced by allergens were also attenuated[[130](#_ENREF_130)]. Vitamin D(VD)-loaded nanoemulsions (VDNM) treatment could effectively decrease MPO activity, oxidative stress, C3 protein level and other proinflammatory cytokines than common forms of VD[[131](#_ENREF_131)]. A new series of fully biodegradable Hydroxybenzyl alcohol (HBA)-incorporated polyoxalate (HPOX) was noticed to its inhibition role to airway inflammation. HPOX nanoparticles reduced intracellular oxidative stress generation and suppression proinflammatory mediators by clearing hydrogen peroxide[[132](#_ENREF_132)]. The microparticles of vanillyl alcohol-containing copolyoxalate (PVAX) could reduce oxidative stress, suppress the levels of pro-inflammatory cytokines (like TNF-α) and iNOS in the lung tissue of OVA challenged asthmatic mice[[133](#_ENREF_133)].

***Non-drug treatment***

Living organisms exposed to a static magnetic field (SMF) may have affects on ROS levels. The ragweed pollen extract may induce allergic inflammation in mice after SMF-exposure; the TAC in mouse airways increased and allergic inflammation decreased; this reaction was time-dependent. Furthermore, SMF could stimulate cellular ROS-eliminating mechanisms[[134](#_ENREF_134)]. Low-level laser therapy (LLLT) has been proven to be an anti-inflammatory therapy and after treatment with LLLT exposure the activity of histone deacetylase of U937 cells could be depressed by activating protein kinase A *via* inhibition of PI3K, which is not reversed by H2O2[[135](#_ENREF_135)]. This result suggests that LLLT could be a potential antioxidative therapy.

***Antioxidant effects of current drugs in asthma***

Corticosteroids are widely used to treat asthma *via* anti-inflammatory effects and are recommended by the GINA guidelines[[136](#_ENREF_136)], and this current asthma therapy has also been found to be effective in preventing oxidative stress. After treatment with inhaled corticosteroids, asthma scores were significantly improved, and Cys-LT and 8-isoprostane concentration in EBC were notably decreased in asthmatic children[[137](#_ENREF_137)]. Inhaled corticosteroid treatment causes significantly lower expression of CYBB mRNA in the NADPH oxidase system[[59](#_ENREF_59)]. Montelukast is a leukotriene receptor antagonist, and plasma total thiol was lower in asthmatic patients that were not given montelukast therapy in comparison to montelukast therapy patients and healthy controls[[138](#_ENREF_138)], although other studies have demonstrated that montelukast therapy resulted in no significant improvement in TOS, TAS and DNA damage parameters[[139](#_ENREF_139)]. Currently, the mechanism of montelukast antioxidative stress remains unclear. Treatment with procaterol, a long-acting β2 agonist, enhances human bronchial epithelial cell viability, while decreasing the percentage of apoptotic cells and reducing MDA and ROS in a dose-dependent manner[[140](#_ENREF_140)].

Ambroxol is used to increase mucociliary clearance and regulate surfactant levels. Clinical studies have reported that ambroxol decreases the levels of protein carbonyls (an oxidative biomarker), increases the level of Th1 cytokines—such as IL-10, IFN-γ, and IL-12-from lung mononuclear cells and alveolar macrophages, but had no effect on Th2 cell cytokines[[141](#_ENREF_141)]. 5-Aminosalicylic acid significantly inhibits the expression of Th2 cytokines, while also decreasing MDA and MPO levels in BALF of mice[[142](#_ENREF_142)].

Sitagliptin and Cinnarizine also reduce proinflammatory cytokine release and inflammatory infiltration, while also restoring GSH and SOD, thus playing a role in reducing airway inflammation and remodeling via antioxidative stress[[143](#_ENREF_143),[144](#_ENREF_144)].

**CONCLUSION**

Asthma is one of atopic diseases which including allergic rhinitis and atopic dermatitis. Low respiratory tract is affected in asthma while other atopic diseases involve other lesions. Airway oxidative stress is a complex condition with important physiological and pathophysiological implications in asthma. Imbalance of the oxidative and antioxidative systems is caused by exogenous and endogenous ROS. Some elevated substances can serve as oxidative or antioxidative biomarkers. Different kinds of treatments have demonstrated antioxidative roles, including diet, vitamin and food supplements, natural extracts, magnetic fields and lasers treatments. However, some of these methods have been unsuccessful due to unforeseen side effects, thus no antioxidants have been applied as first-line therapy in asthma treatment. The choice of antioxidants must be made in regard to individual and environmental factors. More research is required, especially large and well-designed clinical trials, to clarify the clinical value of antioxidant therapy.

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