# Therapeutic Targeting of Oxidative Stress and Inflammation in Asthma and COPD and Pharmacological Interventions with Phytochemicals

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**Abstract**

Asthma and chronic obstructive pulmonary disease (COPD) are the common respiratory diseases posing immense burden on human health. Incidence of asthma and COPD are increasing significantly in recent decade around the world. There is abundant evidence that these disorders are mediated by oxidative stress which plays a key role in the initiation and augmentation of inflammation. Currently available western drugs are associated with severe side effects and resistance, and hence, there is a need of new drugs which can halt the progression of disease. Use of herbal medicine to treat the ailment is known to mankind from ancient times. Phytoconstituents, apart from their antioxidant capacity, possess anti-inflammatory effect. This property can be utilized for the treatment of asthma and COPD, where oxidative stress and inflammation plays a major role in the progression of the disease.

The present chapter deals with the brief explanation of interplay between oxidative stress and inflammation in asthma and COPD. Phytochemicals that showed promising effect against these disorders in the animal models and their molecular mechanism involved for the protection are described briefly.

## 21.1 Introduction

Respiratory diseases pose an immense burden on human health throughout the world. According to the World Health Organization (WHO), chronic respiratory conditions affect more than 1 billion people with an estimated 235 million cases of

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asthma, more than 200 million cases of chronic obstructive pulmonary disease (COPD), 65 million suffering from moderate to severe COPD, over 100 million experiencing sleep-disordered breathing, 8.7 million people ensuing tuberculosis annually and millions living with pulmonary hypertension, and more than 50 million people struggling with occupational lung diseases. Asthma and COPD are the most common obstructive respiratory disorders (World Health Organization 2012, 2013a, b; http://www.who.int/gard/publications/chronic_respiratory_diseases.pdf; http://www.who.int/gard/news_events/1-3.GARD-06-07-K1.pdf). Asthma is a chronic inflammatory disorder of the airways associated with an increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or early in the morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible, either spontaneously or with treatment (Bateman et al. 2008). On the other hand COPD is partially reversible airflow obstruction characterized by the limitation of airflow which is usually progressive and associated with an abnormal response of the lungs to noxious particles or gases (Pauwels et al. 2001). There are some important similarities as well as differences between asthma and COPD (Barnes et al. 2009). Both are chronic inflammatory diseases that involve structural changes in the small airways and cause airflow limitation (Jeffery 1998; Wiggs et al. 1990), resulting from gene-environment interactions and characterized by mucus and bronchoconstriction. However, they both differ in the nature of inflammation and the anatomical sites involved in the disease (Jeffery 1998). Asthma affects only the airways, while COPD affects the airways as well as the parenchyma. Secondly, the nature of inflammation is primarily eosinophilic and CD4-driven in asthma and neutrophilic and CD8-driven in COPD (Keatings et al. 1996a). This later difference affects the response to pharmacological agents as evidenced by the fact that inhaled corticosteroids are effective against the eosinophilic inflammation in asthma but largely ineffective against the primarily neutrophilic inflammation seen in COPD (Keatings et al. 1997). WHO predicts that COPD will become the third leading cause of death worldwide by 2030 (http://www.who.int/gard/news_events/1-3.GARD-06-07-K1.pdf).

Oxidative stress and inflammation play a major role in the pathogenesis of asthma and COPD (Paul et al. 2001; Rahman and Adcock 2006a). Persistent chronic inflammation leads to generation of reactive oxygen species (ROS); prolonged exposure to ROS causes oxidative stress, which leads to overactivity of the immune system (Kleniewska and Pawliczak 2017). Oxidative stress plays a central role in upregulating inflammatory events by activating gene expression of pro-inflammatory cytokines (Zuo et al. 2013). The lung is an organ with large surface area and highly supplied with blood vessels making it susceptible to oxidative damage (Wei Sheg et al. 2014). Both exogenous and endogenous factors play a major role in the production of ROS. Cigarette smoke, vehicle exhaust, gases like ozone, and sulfur dioxide are some of the exogenous factors that play a major role in the production of ROS, whereas the endogenous production of ROS is linked with mitochondria, microsomes, enzymes, and phagocytes. Lungs have a well-defined antioxidant

system to protect against ROS. However, the imbalance between these systems leads to asthma and COPD (Zuo et al. 2013; Sahiner et al. 2011).

Corticosteroids are the effective anti-inflammatory drugs used for the treatment of asthma and COPD; however, they are associated with severe side effects and resistance (Barnes 2006, 2013; Adcock et al. 2008). In recent times much attention is focused on the usage of natural products for the treatment of various disorders because of their minimal side effects associated with them. Natural products show protective effect in various diseases by their antioxidant and anti-inflammatory properties. Several phytoconstituents and extracts have been evaluated for their effectiveness in treating asthma and COPD and were found to be beneficial. In this chapter, we briefly discuss about the role of oxidative stress and inflammation in asthma and COPD, protective effect of phytoconstituents in relevant animal models of asthma and COPD.

## 21.2 Role of Oxidative Stress in Asthma

Generation of ROS is a continuous process which takes place in a cell under normal physiological conditions. Excessive production of ROS shows deleterious effect on a wide range of biological molecules like carbohydrates, proteins, lipids, and mitochondria of cell affecting its function (Gutteridge and Halliwell 2000). There are numerous evidences suggesting that endogenous and exogenous ROS and RNS (reactive nitrogen species) play a major role in the pathogenesis of asthma and factors of asthma severity (Bowler 2004). Asthma is characterized by the presence of amplified levels of RNS and ROS in sputum and breath condensates, which further enhance epithelial permeability, increase mucus secretion, and induce smooth muscle contraction and airway hyperresponsiveness (Rogers and Cismowski 2018). The major enzymatic antioxidants in lungs are superoxide dismutase (SOD), catalase, glutathione S-transferase, and thioredoxin, and nonenzymatic antioxidants include glutathione, cysteine, homocysteine, urate, and ascorbate (Wei Sheg et al. 2014). When ROS overcomes endogenous antioxidant protective response, it leads to deleterious effects and activation of various pathways that have a role in the pathogenesis of asthma (Nadeem et al. 2008).

### 21.2.1 Interplay Between Oxidative Stress and Inflammation in Asthma

There are numerous evidences to prove that overproduction of ROS can evoke inflammatory responses. The inflammatory cells of asthmatics have an increased capability to generate free radicals compared to controls, which further contribute to high concentrations of ROS (Kleniewska and Pawliczak 2017). This is confirmed by the studies that showed increased generation of superoxide anion radicals by inflammatory cells from peripheral blood and bronchoalveolar lavage (BAL) fluid of asthmatic subjects than those from normal controls (Nadeem et al. 2003).

Asthmatic patients demonstrated increased production of ROS by many cell types within the lung including macrophages, antigen-presenting cells (APCs), neutrophils, and eosinophils. On the other hand, ROS can directly stimulate histamine release from mast cells and mucus secretion from airway epithelial cells. ROS are also known to modify the properties of endothelial barrier dysfunction and increase permeability to fluid, macromolecules, and inflammatory cells resulting in bronchial hyperreactivity which is a characteristic of asthma (Park et al. 2009; Rahman and Adcock 2006b).

Oxidants in the lungs which are inhaled or produced by the inflammatory cells act as secondary messengers and activate signal transduction pathways (Lee and Yang 2012). ROS are known to activate the transcription factors like NF-κB and AP-1, which lead to increased inflammatory gene transcription. They play an important role in inflammatory and immune response in most of the cells and are an essential factor that contribute to asthma progression by activating gene coding for pro-inflammatory cytokines (Lee and Yang 2012; Barnes and Adcock 1997). The airways of asthmatic patients have predominant NF-κB activity especially in epithelial cells and macrophages (Imanifooladi et al. 2010) (Fig. 21.1).

#### 21.2.1.1 NF-κB Signaling Pathway

ROS acts as a second messenger for the degradation of IκB, which holds NF-κB in the cytoplasm. Hyperoxic conditions enhance the activation of IKK which leads to enhanced phosphorylation and degradation of IκB promoting the nuclear translocation of NF-κB and its binding to DNA. Many of the inflammatory mediators produced in the airways are regulated by NF-κB pathway, which includes pro-inflammatory cytokines like IL-1β and TNF-α. This pathway also induces genes of many inflammatory cytokines like IL-4, IL-5, IL-9, and IL-15 (Park et al. 2009; Lee and Yang 2012). Further, p50-deficient mice lack the production of IL-4, IL-5, and IL-13 which are supposed to play divergent roles in asthma pathogenesis (Ziegelbauer et al. 2005). Adhesion molecules, such as ICAM-1 (intercellular adhesion molecule-l) and VCAM-1 (vascular cell adhesion molecule-l), are also upregulated by NF-κB pathway (Fig. 21.1). RANTES and eotaxin which attract eosinophils are increased by the activation of NF-κB. Further, the expression of INOS (inducible nitric oxide synthase) is also increased which causes augmented nitric oxide exhalation in asthma patients (Stütz and Woisetschläger 1999; Mori et al. 1999; Sugiura and Ichinose 2008).

#### 21.2.1.2 Activator Protein-1

c-Fos and c-Jun are the other important transcription factors that play a major role in inflammatory process underlying asthma. They dimerize to form homodimeric (Jun/Jun) and heterodimeric (Fos-Jun) complexes of the activator protein (AP)-1 family (Janssen et al. 1997). AP-1 is known to be involved in oxidant signaling, pathogenesis of lung injury, apoptosis, and immune responses (Karin et al. 1997; Shaulian and Karin 2002). AP-1 is also an important contributor to the expression of Th2 cytokines, IL-4, IL-5, and IL-13 (Raju et al. 2014). There is an evidence of augmented c-Fos expression in the epithelial cells of asthmatic patients (Barnes and

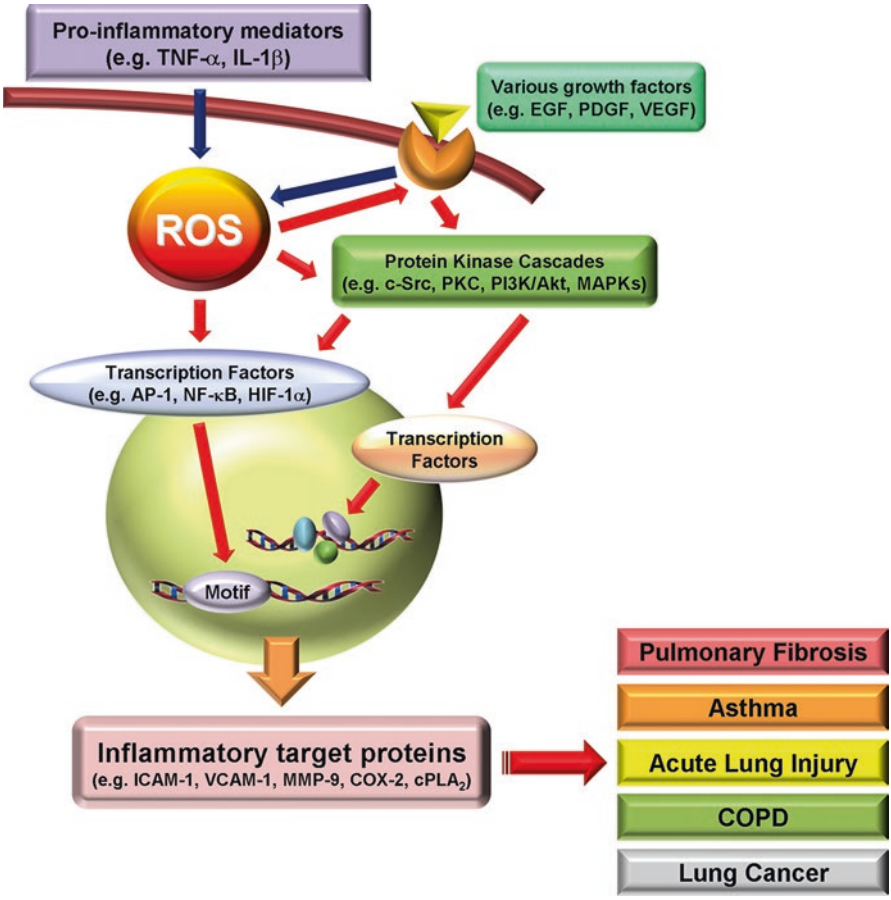


**Fig. 21.1** General overview of the role of ROS in different respiratory diseases which activates transcriptional factors like NF-κB, AP-1, and HIF-1α which in turn produces inflammatory target proteins

Adcock 1998). Studies have indicated that oxidants like $O_2^-$ and $H_2O_2$ can upregulate the transcriptional factors like Fos and Jun (Amstad et al. 1990; Kiyoshi et al. 1991). In a recent study, SIRT 1 (sirtuin 1) decreased c-Fos/c-Jun acetylation, thereby inhibiting the transcription of AP-1 which subsequently reduced the expression of COX-2 and $PGE_2$ (Zhang et al. 2010). In a study, a small molecule inhibitor of redox-regulated NF-κB and activator protein-1 transcription blocked allergic airway inflammation in a mouse model of asthma (Ziegelbauer et al. 2005). These results clearly show that ROS activates AP-1 which in turn produces inflammatory mediators (Fig. 21.2).

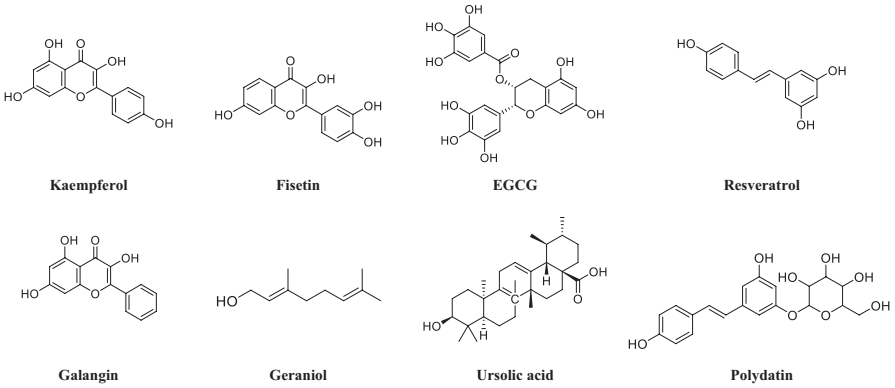


**Fig. 21.2** Structures of phytochemicals effective against asthma

#### 21.2.1.3 Hypoxia-Inducible Factor 1

Hypoxia-inducible factor 1 (HIF-1) is a heterodimeric transcription factor, which is made up of two subunits HIF-1α and HIF-1β. HIF-1β is constitutively expressed, whereas HIF-1α is degraded by ubiquitin-protease system; under hypoxic conditions this subunit is stabilized, and it is translocated into the nucleus and induces hypoxia-responsive genes like inflammatory genes and VEGFA (vascular endothelial growth factor A) (Lee et al. 2007). ROS increase vascular permeability by inducing VEGFA expression through upregulation of HIF-1α (Lee and Yang 2012). ROS have also been known to stabilize HIF-1α under hypoxic or non-hypoxic conditions and promote its translocation into the nucleus (Lee et al. 2006). Haddad et al. reported that TNF-α increased the accumulation of ROS and activation of HIF-1α (Haddad and Land 2001). HIF-1α levels are increased when they are exposed to ROS and the levels are decreased when they are subjected to antioxidants (Park et al. 2009).

## 21.3 Oxidative Stress Markers in Asthma

Direct measurement of free radicals is difficult because of their short-lived nature. It is well known that overproduction of ROS has detrimental effects on biological molecules like lipids and protein. Therefore, oxidative stress is measured indirectly by studying its effects on the biomolecules.

The most studied markers are isoprostanes, malondialdehyde (MDA), myeloperoxidase (MPO), and thiobarbituric acid. The markers of protein damage studied are nitrotyrosine and bromotyrosine (Nadeem et al. 2008). Isoprostanes are prostaglandin-like molecules which are produced during oxidative damage on polyunsaturated fatty acids (PUFA) present in the cell. Some of the isoprostanes increase airway hyperresponsiveness (AHR) and smooth muscle constriction; apart from these effects, isoprostanes (8-iso-$PGF_{2\alpha}$) can also enhance the binding of macrophages to endothelial cells and stimulate the secretion of IL-18 by regulating

mitogen-activated protein kinase (MAPK) pathway. They are present in detectable amounts in the biological fluids and unaffected by fat in the diet. Asthma is characterized by increased lipid peroxidation as evident from increased level of isoprostane 8-iso-$PGF_{2\alpha}$, in asthmatics compared to normal group. Further evidences include the urinary excretion of isoprostane in the urine of mild atopic asthmatics (Voynow and Kummarapurugu 2011). It is reported that increased levels of isoprostane 15-$F_{2t}$-isoP were observed in serum and urine samples of asthmatics compared to normal people (Wedes et al. 2009).

MDA is a product of lipid peroxidation which is a consequence of oxidative stress (Wood et al. 2003). The levels of MDA are measured in blood, sputum, bronchoalveolar lavage fluid, and exhaled breath condensate (EBC). MDA levels in EBC are high in asthmatics compared to normal (Nadeem et al. 2008). Ethane, another product of lipid peroxidation, is also upregulated in asthmatics (Paul et al. 2001). Further more, the damaged lipids alter the structure of structural proteins in the cell membrane, which leads to proteolytic degradation (Yao and Rahman 2011a).

## 21.4 Animal Models of Asthma

Animal models of asthma are required to understand the pathophysiology of the disease and to study the efficacy of compounds against it. Several species like mice, rats, guinea pigs, and primates are used in the studies, and different methods are used to induce the asthma in these animals (Zosky and Sly 2007; Stevenson and Belvisi 2008). Some of the commonly used methods are described below.

### 21.4.1 Ovalbumin-Induced Model of Asthma

Ovalbumin (OVA)-induced allergic inflammation is the most commonly used model to study asthma. OVA is an antigen present in egg whites, which is administered along with an adjuvant to enhance immunogenicity. The most frequently used adjuvant are aluminum hydroxide or alum and ricin. A usual protocol would be sensitization of animals to OVA along with adjuvant through i.p route. The second dose can be given 1–2 weeks later; this is followed by sensitization of OVA to the airways generally by aerosols. The animals develop AHR in 24–48 h. In this model, there is an increased IgE level, Th2-subtype cytokine secretion, bronchoconstriction, edema, and increased mucus secretion which are characteristic features of asthma. The main limitation of the model is the development of tolerance on chronic exposure of OVA [53 54].

### 21.4.2 House Dust Mite Model of Asthma

House dust mite (HDM, *Dermatophagoides* sp.) is the common allergen worldwide; 50–85% of asthmatics are HDM allergic (Gregory and Lloyd 2011). HDM

extracts have different allergens and contribute to its allergic lung inflammation. The model is advantageous over OVA induced asthma, in that, the model can replicate the features of chronic asthma and airway remodeling upon longer exposure to HDM. Asthma-like features, i.e., increased IgE and increased APC, lymphocytes and eosinophils are reported to develop by administering HDM intranasally for 10 days (Mullane and Williams 2014; Stevenson and Birrell 2011).

## 21.5 Phytochemicals Effective Against Asthma

### 21.5.1 Kaempferol

Kaempferol is a flavonoid, a polyphenolic compound commonly present in medicinal plants like *Euphorbia pekinensis* Rupr., *Ginkgo biloba* L., *Hypericum perforatum* L., *Phyllanthus emblica* L., *Ribes nigrum* L., and *Rosmarinus officinalis* L. It is also present in apples, tomatoes, broccoli, grapes, and other edible foods. The protective role of kaempferol is well studied. It is an antioxidant, anti-apoptotic, and anti-inflammatory compound (Calderon-Montano et al. 2011). Gong et al. reported abrogation of eosinophil deposition and degranulation in lung tissue of ovalbumin (OVA)-induced asthma in mice by kaempferol treatment through downregulation of NF-κB pathway (Gong et al. 2011). Chung et al. evaluated the effect of kaempferol and kaempferol-3-O-rhamnoside, water-soluble form of kaempferol on OVA-challenged mice; results demonstrated that pretreatment of kaempferol inhibited Th2-related cytokine level (IL-4, IL-5, and IL-13) by antioxidant effect. In contrast, kaempferol-3-O-rhamnoside had lower antioxidant effect compared to parent kaempferol but showed higher inhibitory effect on Th2 cytokines, TNF-α level, and IgE production (Chung et al. 2015).

### 21.5.2 Fisetin

Fisetin is a flavonoid present in foods including fruits like strawberry and apple and vegetables like onions and cucumber (Sung et al. 2007). It has demonstrated diverse beneficial effects like antioxidant, anti-inflammatory, neuroprotective, anticancer, antidiabetic, antiviral, as well as anti-angiogenesis effects in both in vitro and in vivo models. In a study, prophylactic treatment with fisetin in OVA-challenged mice decreased airway hyperresponsiveness, mucus hypersecretion, and Th2 cytokine level (IL-4, IL-5, and IL-13) in bronchoalveolar lavage fluid which was increased during OVA administration. Fisetin markedly inhibited p65 nuclear translocation, thereby inhibiting NF-κB pathway. These results corroborated with in vitro study on human lung cell lines where fisetin suppressed NF-κB reporter gene expression (Goh et al. 2012).

### 21.5.3 Epigallocatechin Gallate

Epigallocatechin gallate (EGCG) is a catechin present in green tea leaves, oolong tea, and black tea leaves. It has antioxidant and anti-inflammatory properties and is proven effective in disorders of the cardiovascular system, ulcerative colitis, kidney disorders, and cancer (Eng et al. 2017). Kim et al. reported the protective effect of EGCG on toluene diisocyanate-induced airway inflammation in a murine model of asthma; treatment with EGCG reduced the generation of ROS and MMP-9 expression; decreased the number of inflammatory cells like eosinophils, macrophages, and neutrophils; and reduced the level of TNF-α in BAL fluids (Kim et al. 2006). In another study on OVA-induced asthma in mice, EGCG reduced the count of neutrophils and eosinophils in BAL; decreased airway resistance; decreased cytokine levels of IL-4, IL-6, and TNF-α; and improved proportion of Th17/Treg cells and exerted its effect through TGF-β1 signaling pathway (Shan et al. 2018).

### 21.5.4 Resveratrol

Resveratrol is a polyphenolic compound present in families like Vitaceae, Dipterocarpaceae, Gnetaceae, Cyperaceae, and Leguminosae. It is present in various food and food products such as grapes, wine, grape juice, mulberries, and cranberries (Pangeni et al. 2014). The effect of resveratrol against house dust mite (HDM)-induced asthma was studied in a mouse model. Treatment with resveratrol decreased the levels of IL-6, IL-17, TNF-α, and TGF-β in BALF which were upregulated in HDM-treated mice per se. It also suppressed the IgE-induced expression of Syk (spleen associated tyrosine kinase) in RBL-2H3 cells (Chen et al. 2015). In another study on OVA-induced asthma, administration of resveratrol decreased 8-isoprostane level by its antioxidant effect and decreased activation of PI3K-Akt signaling by restoring the expression of INPP4A (inositol polyphosphate 4-phosphatase) (Aich et al. 2012).

### 21.5.5 Galangin

Galangin belongs to chemical class of flavanol, mainly present in medicinal plants *Alpinia officinarum* and *Helichrysum aureonitens* and foods like honey. It has various pharmacological properties like anti-inflammatory, antioxidant, and anti-fibrotic (Mak et al. 2018). Zha et al. studied the effect of galangin on TNF-α-stimulated human ASMC (airway smooth muscle cells); they also studied the effect of galangin on OVA-induced asthma. The results of their study demonstrated that galangin inhibited the NF-κB pathway in TNF-α-stimulated human ASMC, whereas it decreased Th2 cytokine (IL-4, IL-5, and IL-13) levels in BALF, decreased IgE, and suppressed NF-κB activity in OVA-induced asthma (Zha et al. 2013). Another study reported that treatment with galangin attenuated TGF-β-induced ROS production in human ASMC and decreased OVA-specific IgE level in serum as well as reduced

α-SMA and MMP-9 expression and VEGF and TGF-β1 expression in OVA-induced asthma model (Liu et al. 2015).

### 21.5.6 Geraniol

Geraniol is a monoterpene alcohol present in geranium, lemon, and other essential oils in medicinal plants. Previous studies reported the antioxidative, antimicrobial, antitumor, and anti-inflammatory activities of geraniol (Lei et al. 2018). Xue et al. reported the protective effect of geraniol in OVA-induced asthma. Geraniol increased Nrf-2 expression and increased GST and SOD activities in OVA-challenged mice showing its antioxidant effect by decreasing oxidative stress through Nrf2/ARE pathway as well as improving Th1/Th2 balance in lungs (Xue et al. 2016).

### 21.5.7 Polydatin

Polydatin is a glucoside mainly extracted from the plant *Polygonum cuspidatum*, a natural antioxidant known to have many medicinal properties. Polydatin is well known for its anti-inflammatory, analgesic, cardioprotective, and antitumor activities (Du et al. 2013). Polydatin was evaluated against OVA-induced asthma in a mouse model; OVA-treated mice showed increased ROS and TGF-β and decreased Nrf-2 activity. However, polydatin treatment enhanced the antioxidant NQO1 enzyme activity and increased Nrf2 and HO-1 expression. These results conclude that polydatin effectively decreased the ROS production and fibrosis by increasing Nrf2 activation (Zeng et al. 2018).

### 21.5.8 Ursolic Acid

Ursolic acid (UA) is a pentacyclic triterpenoid carboxylic compound present in many medicinal plants, belonging to Lamiaceae family. UA is known for its hepatoprotective, cardioprotective, antitumor, antidiabetic, and inflammatory properties (López-Hortas et al. 2017). Kim et al. reported the protective effect of ursolic acid against ovalbumin-induced asthma by decreasing the influx of inflammatory cells in BAL and the level of Th2 cytokines and IgE (Kim et al. 2013).

## 21.6 Oxidative Stress in COPD

COPD is characterized by progressive airflow obstruction that is generally not reversible. Smoking is the major risk factor for COPD; each puff of cigarette smoke includes $10^{17}$ oxidants/free radicals (Church and Pryor 1985). Once the disease is established, the production of ROS doesn't halt even after the cessation of smoking due to generation of ROS from mitochondrial respiration. Other factors like air

pollution, occupational dust, and infections exacerbate COPD (Białas et al. 2016). One of the major factors for the pathogenesis of COPD is the imbalance between oxidants and antioxidants (Domej et al. 2014). There are numerous markers like $H_2O_2$ and 4-hydroxy-2-nonenal to identify the ROS-induced damage in COPD. Many studies have confirmed that markers of oxidative stress are increased in the lungs and systemically (blood) in COPD patients. Hydrogen peroxide concentration is increased in the exhaled breath of smokers with COPD compared to non-smokers (Rahman 2005). A product of lipid peroxidation, 4-hydroxy-2-nonenal, is seen higher in the bronchial secretions of COPD patients as compared to the normal control, and its level is elevated in the smokers without COPD compared to non-smokers. Sputum of COPD patients had increased concentration of nitrotyrosine compared to healthy controls and asthmatics (Petruzzelli et al. 1997). The TBARS concentration is increased in lungs and breath condensate in COPD patients. Moreover ROS has deleterious effects on nucleic acids; 8-hydroxyguanosine (8-OHG) is the oxidized product of RNA and is prevalent in lung tissue of emphysema (Fischer et al. 2011).

The human body has an antioxidant defense mechanism to prevent the damage caused by ROS. Numerous enzymes for detoxification of aldehydes are increased in mice subjected to cigarette smoke. The total antioxidant capacity in COPD patients is decreased compared to normal control. In a study there was a decrease in the mRNA of GSTP1 (glutathione S-transferase P), GSTM1 (glutathione S-transferase mu 1), EPHX (epoxide hydrolase 1), and TIMP2 (tissue inhibitor of metalloproteinases) in lung tissues of COPD subjects (Yao and Rahman 2011b). Several studies have shown a clear association between reduced levels of the antioxidants in the lungs, such as tocopherol and ascorbic acid, and deteriorating pulmonary function in COPD (Rahman 2005). Nrf-2 is a transcription factor which regulates antioxidant proteins. A study indicated that exposure of cigarette smoke to Nrf-2-deficient mice had amplified inflammation, apoptosis, and exacerbated emphysema. Nrf2 and Nrf2 activators have great prospective for shielding against RNS in tobacco smoke, particularly in COPD patients (Tuder et al. 2006).

The consequence of ROS is imbalance of protease/anti-protease in the lungs, which is observed in the emphysema. There is an amplified burden of elastase on the lungs due to deficiency of α1-antitrypsin. A study indicated that cigarette smoke can inactivate anti-proteases. As a result there is significant accumulation of macrophages and neutrophils which can release proteases like matrix metalloproteinases (MMP) and cathepsins which guide the degradation of α1-antitrypsin. Cigarette smoke is implicated to have a role in the apoptosis of pulmonary endothelial cells and apoptosis is an early event occurring in alveolar tissue devastation in the emphysema (Rahman 2005; Fischer et al. 2011).

### 21.6.1 Interplay of Oxidative Stress and Inflammation in COPD

Inflammation in COPD is not a separate thing by itself but is integrally related to oxidative stress. Inflammation is characterized by release of pro-inflammatory

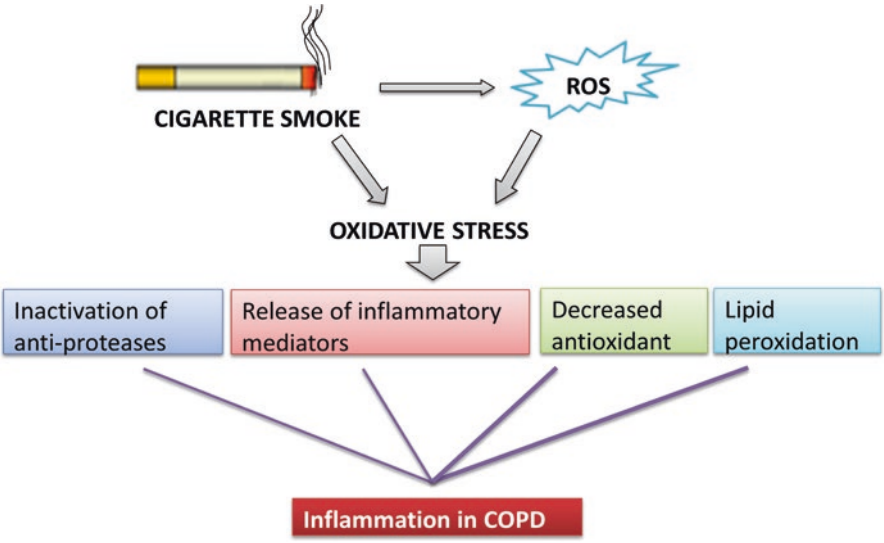


**Fig. 21.3** Mechanism of ROS-mediated lung inflammation in COPD. Oxidative stress generated causes inactivation of anti-proteases and, release of inflammatory mediators and lipid peroxidation products leads to inflammation in COPD

mediators in the lung by neutrophils, B-cells, macrophages, T-cells, eosinophils, and mast cells (Rennard and Barnes 2002). Oxidants in cigarette smoke can trigger macrophages to produce ROS, which can magnetize neutrophils in the lungs (Fig. 21.3).

It is reported that circulating neutrophils release more $O_2$ in smokers and COPD patients (Rennard and Barnes 2002). It has been studied that immune cells of COPD patients release more proteases in sputum and BAL than normal control. Neutrophils secrete several proteinases, including neutrophil elastase (NE) and cathepsin G which add to parenchymal devastation. Neutrophil deformability was increased by oxidants and enhanced its sequestration to the endothelial cells of blood vessels in the lungs (Fischer et al. 2011). Chronic inflammation evidenced by increased levels of IL-1β, IL-6, CXCL8/IL-8, GM-CSF, and TNF-α secreted by macrophages exposed to cigarette smoke is the characteristic feature of COPD (Yao and Rahman 2011b).

### 21.6.2 Inflammation and Gene Expression

There is an increase in concentration of TNF-α and IL-8 in the sputum of COPD patients. The genes for these inflammatory mediators are regulated by NF-κB pathway. There is an augmented expression of p65 protein of NF-κB in the epithelial cells of lungs in smokers and COPD patients (Keatings et al. 1996b). Many stimuli can trigger the activation of NF-κB; one of the stimuli is cigarette smoke. Cigarette smoke

and extracts of cigarette smoke can activate NF-κB in immune cells. Smokers with COPD and currently healthy smokers both increase DNA binding activity of NF-κB causing an increased release of inflammatory mediators such as nitric oxide, IL-8, IL-1, and prostaglandins thereby upregulating COX-2 enzyme (Rom et al. 2013).

### 21.6.3 Histone Modifications

Acetylation of histone proteins results in uncoiling of the DNA, thereby allowing transcription factor binding leading to gene transcription. Histone acetylation can be reversed by deactivating histones through removal of acetyl group. Histone deacetylases (HDAC) suppress gene expression by switching off gene transcription through recruiting co-suppressor proteins (Barnes 2009). In COPD, in peripheral lung airway biopsies, and in alveolar macrophages, there is a raise in the acetylation of histones coupled with the promoter region of inflammatory genes, such as IL-8, that are regulated by NF-κB, and the scale of acetylation increases with disease severeness. HDACs also have the capability to deacetylate non-histone proteins, such as NF-κB, thus modifying NF-κB-dependent pro-inflammatory gene transcription (Szulakowski et al. 2006). HDAC-2, one of the isoforms of HDAC, is necessary for the immunosuppressive actions of glucocorticoids. Reduced level of HDAC-2 is associated with increased pro-inflammatory response and reduced responsiveness to glucocorticoids in alveolar macrophages obtained from smokers (Ito et al. 2001). Thus cigarette smoke/oxidants not only decrease the activity of HDAC-2 in the macrophages and epithelial cells but also decrease the functions of glucocorticoids in COPD patients. Oxidative stress plays a major role in decreasing the activity of HDAC-2 by posttranslational modification which leads to proteolytic degradation of HDAC-2 (Adenuga et al. 2009).

### 21.6.4 Sirtuin 1

SIRT-1 (sirtuin 1) is the most studied human sirtuins reported to possess many physiological actions like anti-apoptotic, anti-inflammatory, and antiaging properties. SIRT-1 is a HDAC that removes acetyl group on the histones and silences the gene transcription (Rahman et al. 2012). The level of HDAC is affected by posttranslational modifications, oxidants, and aldehydes derived from lipid peroxidation which causes SIRT-1 phosphorylation in macrophages and mouse lungs (Caito et al. 2010). Increased activation of NF-κB is seen when SIRT-1 has been knocked down using siRNA; SIRT-1 also suppressed the activation of activator protein-1 which leads to downregulation of COX-2 enzyme suggesting that modulation of SIRT-1 can be a therapeutic target for COPD (Rajendrasozhan et al. 2008). Nrf-2 is the other transcription factor present in cell which imparts protection against ROS produced from cigarette smoke. Nrf2 activation leads to upregulation of many antioxidant genes and there is a decreased activation of Nrf-2 in the patients suffering from COPD (Tuder et al. 2006). Many phytochemicals can activate Nrf-2 and can protect against

deleterious effects of ROS. Combining Nrf-2 activators with other therapeutic drugs to treat COPD will have positive effects.

## 21.7 Phytochemicals in Protection Against COPD

### 21.7.1 Curcumin

Curcumin is a yellow-colored compound present in *C. longa* and is a perennial member of the Zingiberaceae family. Curcumin is a well-explored phytochemical for various pharmacological activities (Gupta et al. 2013). Curcumin inhibited PPE (porcine pancreatic elastase)-induced inflammation and emphysema by increasing antioxidants and inhibiting chemokine secretion. In another model with cigarette smoke, curcumin decreased the number of inflammatory cells in BAL and decreased protein carbonyl levels, indicator of oxidative stress in BALF (Suzuki et al. 2009). Jin et al. reported the protective effect of curcumin against LC (LPS and cigarette smoke)-induced COPD in a mouse model and LPS-stimulated BEAS-2B cells in vitro (Yuan et al. 2018).

### 21.7.2 *Trans*-Anethole

Trans-anethole, the major constituent obtained from anise, star anise, and fennel, has been reported to have anti-inflammatory, antioxidant, anticarcinogenic, neuroprotective, and vasoactive effects. In PPE/LPS (porcine pancreatic elastase/lipopolysaccharide)-induced COPD mouse model, pretreatment with anethole decreased the level of LDH (lactate dehydrogenase) in the BAL of animals, which was increased in PPE/LPS alone treated group of animals. The number of inflammatory cells like lymphocytes, neutrophils, and macrophages are increased in the PPE-/LPS *per se* treated group than in control group. Pretreatment with anethole significantly decreased the count of inflammatory cells. Pro-inflammatory cytokine levels are measured by ELISA which indicated the increased level of these cytokines in PPE/LPS group compared to control group and pretreatment with anethole decreased the level of these cytokines (Kim et al. 2017).

### 21.7.3 Andrographolide

Andrographolide, one of the diterpenoids, is purified from the aerial parts of plants of the genus *Andrographis*. Andrographolide is known to possess hepatoprotective, antiviral, anticancer, anti-inflammatory, and antithrombotic effects. Andrographolide has been studied against cigarette smoke-induced lung injury in mice. Andrographolide significantly decreased the total inflammatory cells and neutrophils. It suppressed the gene expression of GM-CSF (granulocyte-macrophage colony-stimulating factor), TNF-α, and MIP (macrophage inflammatory protein)-2α

and also decreased the levels of IL-1β, IP-10 (interferon gamma-induced protein), MCP-1 (monocyte chemoattractant protein), and KC (keratinocyte chemoattractant) in BALF, which were upregulated by exposure to cigarette smoke. Andrographolide markedly suppressed the levels of 3-NT (nitrotyrosine), 8-OHdG, and 8-isoprostane ameliorating oxidative damage to proteins, DNA, and lipids induced by cigarette smoking. Andrographolide by its antioxidant property promoted the GSH-related enzyme activity as well as increased the nuclear Nrf-2 levels (Guan et al. 2013).

### 21.7.4 Quercetin

Quercetin is a 3,3′,4′,5,7-pentahydroxyflavone found in many plants. Due to its polyphenol structure, quercetin has potent antioxidant effects. A broad spectrum of beneficial properties have been described for quercetin, including anti-inflammatory effects, atherosclerosis, thrombosis, hypertension, and arrhythmia. Quercetin was tested against elastase-/LPS-induced lung injury which showed features of COPD in mice (Fig. 21.4).

Elastase-/LPS-exposed mice treated with vehicle showed significantly increased levels of TBARS and iNOS, decreased levels of HMOX-1 (heme oxygenase-1) mRNA, and decreased ratio of *iNOS/HMOX-1*. In contrast, elastase-/LPS-exposed mice treated with quercetin showed significantly reduced TBARS, increased HMOX-1 mRNA, and decreased *iNOS/HMOX-1* compared to vehicle-treated controls. These results demonstrated the antioxidant effect of quercetin. Quercetin treatment of elastase-/LPS-exposed mice inhibited the MMP-9 and MMP-12 activities and increased both Sirt1 mRNA and protein levels. Quercetin treatment also decreased the levels of all chemokines and pro-inflammatory cytokines (Ganesan et al. 2010).

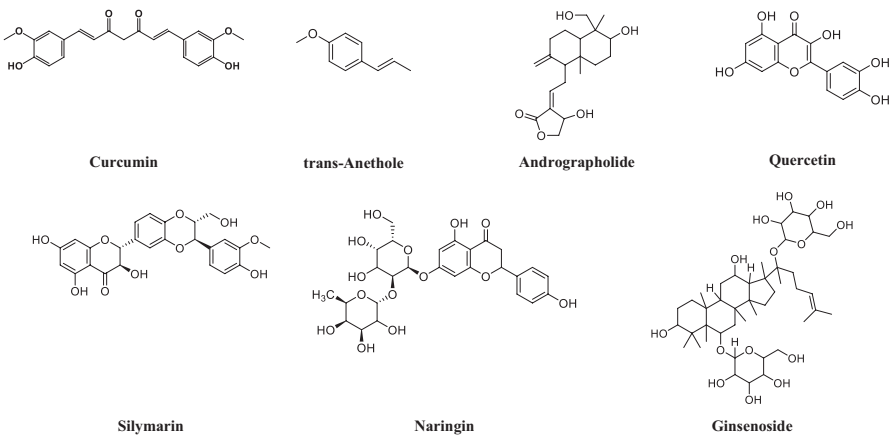


**Fig. 21.4** Structures of phytochemicals effective against COPD

### 21.7.5 Silymarin

Silymarin is a flavonoid extracted from milk thistle (*Silybum marianum*) and has been extensively investigated for antioxidant, anti-inflammatory, anti-apoptotic, and anti-fibrotic properties. Silymarin is also studied against CS-induced airway inflammation. BALF of CS-treated mice per se had increased number of macrophages and neutrophils, whereas silymarin treated along with CS exposure decreased these inflammatory cells in BALF. Further, the pro-inflammatory cytokine levels (TNF-α, IL-1β, and IL-8) increased in CS-treated mice, and silymarin pretreatment decreased the levels of these cytokines. In conclusion silymarin had protective effects by inhibiting ERK/p38 MAPK pathway (Li et al. 2015). In another study silibinin, a major active component of silymarin, was studied and inhibited the pulmonary fibrosis in CS- and LPS-exposed mice by suppressing TGF-βb1/Smad 2/3 pathway (Ko et al. 2017).

### 21.7.6 Ginsenoside Rg1

Ginsenoside Rg1 is a major ginsenoside present in *Panax ginseng* and is known for many pharmacological properties like antiaging, immunoregulation, neuroregulation, lipid regulation, anti-thrombosis, and wound healing (Kim 2017). Ginsenoside Rg1 was studied against CS-induced COPD in rats. The results indicated that ginsenoside Rg1 decreased the pulmonary fibrosis by decreasing the expression of α-SMA (smooth muscle actin) and E-CAD (cadherin) partly by inhibiting TGF-β1/Smad pathway. Similar findings were observed in HBE cells exposed to CSE (Guan et al. 2017).

### 21.7.7 Naringin

Naringin is a flavonoid abundantly present in grapes and citrus family and is known to possess protective actions against hepatotoxicity, radiation-induced damage, ischemia reperfusion injury, neuroprotection, and nephrotoxicity. Naringin was studied for its effect on airway inflammation in a guinea pig model of chronic bronchitis induced by cigarette smoke. With repeated exposure to CS-induced cough, however, oral administration of naringin suppressed cough and reduced inflammatory cells in the lung tissue. Further, naringin markedly reduced the levels of IL-8, TNF- α, LTB4, and the MPO activity in BALF. Naringin dose dependently increased the levels of SOD, which was significantly decreased in the rats exposed to CS (Luo et al. 2012).

## 21.8 Conclusion

Despite the significant therapeutic effect of the synthetic drugs in the respiratory diseases like asthma and COPD, they are associated with resistance and severe adverse effects in many patients. Since ancient times, natural products are well known for their medicinal properties, which led to a paradigm shift toward phytochemicals for the development of new drugs. Phytochemicals of several classes like alkaloids, terpenoids, and polyphenols were evaluated against asthma and COPD, beyond their antioxidant property, and these compounds have shown profound anti-inflammatory property in the preclinical animal studies. These phytochemicals can be used in combination with other anti-inflammatory drugs or can be used alone in the treatment of asthma and COPD, allowing a decline in adverse drug reactions and cost. Further studies have to be conducted to judge their efficacy and safety for human use.

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