Novel Paradigms Of Drugs For Regimen Of Chronic Obstructive Pulmonary Disease

Ankur Rohilla[1], Seema Rohilla[2*], Mohd Masih Uzzaman Khan[3]

[1]Departmentof Pharmaceutical Sciences, Universal Group of Institutions, Dera Bassi-140501, Mohali, Punjab, India.
[2*]Department of Pharmacy, Panipat Institute of Engineering and Technology,Panipat-132103, Haryana, India.
[3]Department of Pharmaceutical Chemistry and Pharmacognosy, Unaizah College of Pharmacy, Qassim University, Unaizah 51911, Saudi Arabia

***Corresponding Author:-** Dr. Seema Rohilla
Department of Pharmacy, Panipat Institute of Engineering and Technology,Panipat-132103, Haryana, India
E-mail: seemarohilla4@gmail.com

Abstract
Chronic obstructive pulmonary disease (COPD) refers to a collection of ailments that are responsible for blockage of airflow and breathing problems like chronic bronchitis and emphysema, resulting in extreme respiratory distress. The seriousness of the illness helps to determine which medicines are utilized for its treatment. In initial stages of COPD, people with severe respiratory issues need to take medicine. Certain medications must be administered regularly when the symptoms recur and worsen. When COPD becomes complex, patients need to take multiple drugs simultaneously. Conventional and nanoforms of several drugs like bronchodilators, N-acetyl-L-cysteine (NAC), Nrf2 activators, spin traps, anti-inflammatory drugs, and enzyme mimics that are used to fight against the oxidative stress are discussed in this review. It also highlighted the significance of the nanocarriers and microparticles in treating chronic lung disease along with stem cell and gene therapy related approaches. In short, this review article highlights the pathophysiology and various treatment options for COPD.

Keywords: Chronic obstructive pulmonary disease, Respiratory distress, Nanocarriers, Gene therapy, Pathophysiology.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is an ailment symbolized by persistent restriction in lung airways. The World Health Organization (WHO) forecasts that COPD will rank third among all causes of death globally by the year 2030. Oxidative stress, an allergic reaction, and modifications to biological purposes like cell propagation, altered programmed cell demise, and cellular degeneration are some of the elements that led to the pathophysiology of COPD. The foremost factor in aetiology of COPD is oxidative stress. Reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are produced by stimulated neutrophils and macrophages, as well as endogenous sources like cigarette smoke (CS) and air pollution, all were contributed to the rise in oxidative burden on the lungs. The destructive oxidants produced by cigarette smoke are inhaled by the people may cause COPD due to discrepancy between antioxidant and oxidant species. Consequently, strong therapeutic drugs used to treat ailments of lungs have ability to increase endogenous antioxidant efficiency or change the redox system to decrease the oxidative stress [1-2]. The present review explored several traditional and different antioxidants like Nrf2 activators, N-acetyl-L-cysteine (NAC), spin traps, and enzyme mimics that are used to fight against the oxidative stress. An important function of the transcription factor Nrf2 is to trigger the Antioxidant Response Element (ARE), which regulated the expression of several Phase II antioxidant genes. Sulforaphane, curcumin, terpenoids, and others are potential Nrf2 activators [3]. A few examples of enzyme mimics that mimic the natural actions of several antioxidant enzymes include superoxide dismutase, catalase, and glutathione peroxidase. These nanocarriers can also be combined with a range of targeting ligands that are specific to receptors found in diseased cells, enabling focused delivery while reducing the drug side effects. The targeted delivery of medicines based on genes and stem cells can be accomplished with the help of nanocarriers. The significance of the nanocarriers and microparticles in treating chronic lung disease along with stem cell and gene therapy related approaches are also discussed.

2. Pathophysiology of COPD

Chronic inflammation, excessive free radical formation, and oxidative and nitrosative stress are all factors contributed in the aetiology of COPD (**Fig 1**). The primary aspect of COPD that affects the pulmonary parenchyma and peripheral airway system is chronic inflammation [4]. COPD triggers like pollutants, smoking, and biomass initiated the allergic reaction by enhancing

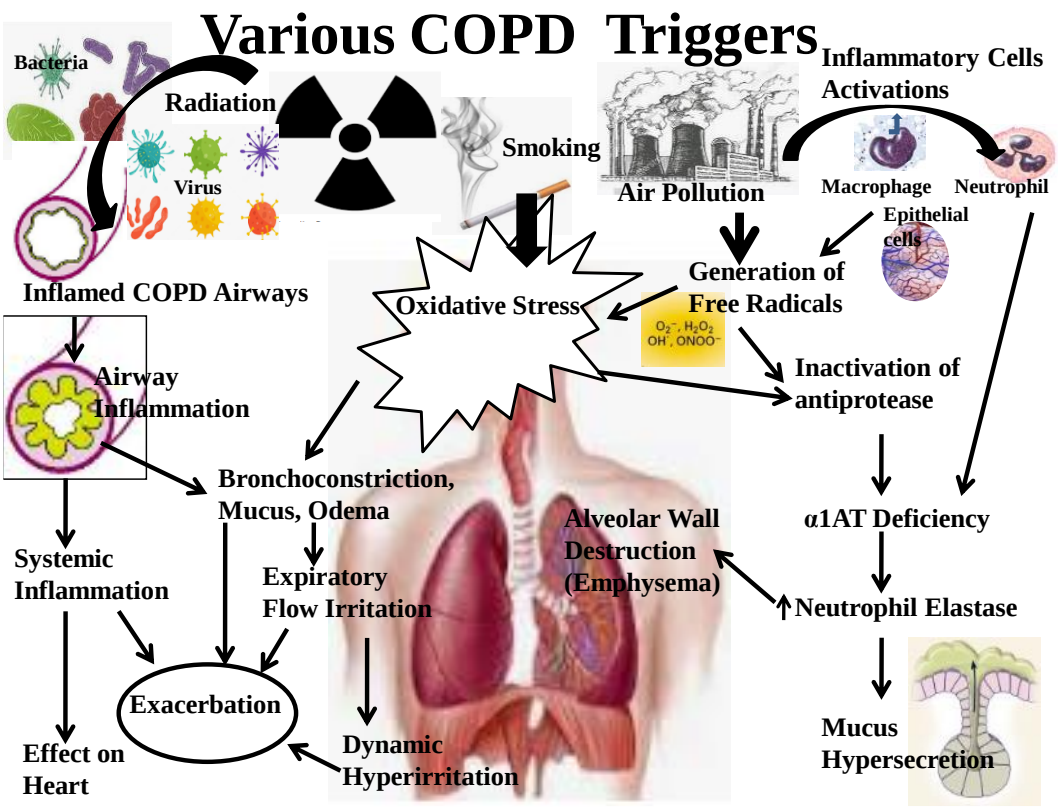

Fig 1: Pathophysiology of COPD

the appearance of inflammation-related mediators. These intermediates are synchronized by the transcription factors NF-κB and p38 map kinase (MAPK) [5]. As a result, innate immune cells such macrophages, neutrophils, and lymphocytes were quickly activated. After sometimes, a significant amount of adaptive immune cells, like CD8+ cytotoxic and CD4+ helper T cells, drift to the lungs and increased the cellular inflammation [6]. Asthma is developed in some patients due to augmentation in the amount of eosinophil cells in airways. In the lung airways, cells such as epithelial cells, macrophages, and neutrophils regulated the release of different proteases that destructed the elastin fibres. It increased the discharge of mucus in COPD patients by motivating the neutrophil elastases. Emphysema is caused by metalloproteinases such MMp9 and MMp12, which endorsed elastolysis in lung parenchymatous tissues. The airway inflammation in people with normal lung function is increased due to consistent exposure to smoke. The conditions of patients become worsen during mild exacerbations in COPD patients because of decline in capacity of enzyme nuclear histone deacetylase 2 and the presence of macrophages in the lungs [7]. Haemophilus influenza and Streptococcus pneumonia made colonies in the lower respiratory tract and exacerbates soreness in patients of COPD [8]. Due to this, bacteria and apoptotic cells were not undergo phagocytosis appropriately by macrophages and impaired the lung inflammation [9]. Due to this reason inflammation persists even after cessation of smoking.

Due to cigarette smoke inhalation, patients with COPD experience severe oxidative stress that is exacerbated by the activation of neutrophils and macrophages. Reactive oxygen species (ROS) or free radicals, which contribute significantly to oxidative stress and hyper inflammation, exacerbate the pathogenesis of COPD. p38 MAPK and NF-κB were activated by ROS, and this increased the manifestation of genes and proteins associated with the process of inflammation. ROS suppressed the severe elastolysis caused by antiprotease 1-antitrypsin. According to Nakamaru et al., oxidative stress caused irreversible DNA damage and is therefore expected to augment the threat of developing lung tumors [10]. Production of ROS encouraged carbonylation of proteins in COPD patients that leads to development of auto-antibodies. These antibodies circulated in systemic circulation, penetrated through the lung mucosa and aggravated the inflammatory response. Pulmonary tissue fibrosis is caused by ROS-mediated stimulation of transforming growth factor (TGF). Nuclear transcription factor (NRF) played a significant role in synchronizing the equilibrium of cytoprotective and antioxidant genes due to oxidative stress; however, activity of NRF_2 in COPD patients were reduced due to enhanced acetylation and a decrease in HD_2 activity [11].

Recent research shows that mitochondrial dysfunction causes a decrease in endogenous ATP and oxidative phosphorylation in COPD patients. Tanner and Single mimicked the cigarette smoke *in vitro* to investigate how cell degeneration and ROS excessive production enhanced the disintegration of mitochondria in COPD patient's epithelial cells. In epithelial cells of the lung tissues, cigarette smoke induced mitochondrial autophagy/mitophagy [12].

3. Non-drug therapy

In order to enhance the quality of life while decreasing the probability of exacerbations, the consequence of symptoms, and decreasing functional ability, non-drug interventions are just as crucial as pharmacotherapy [13]. According to McDonough, the best way to improve one's life quality and decreasing the probability of death due to lung ailment is to

stop smoking [14]. Pulmonary rehabilitation is a vital mediation to maximize the capacity to do exercise. It involved a planned exercise program along with self-management techniques, symptom control, and suitable education. This is usually implemented in direct superintendence of a skilled person. Continuance of physical activity is mandatory for sustaining the advantage of pulmonary rehabilitation alone.

4. Drug therapies

4.1 Conventional Drug Therapies

There is no evidence that pharmacological therapy, other than oxygen has been demonstrated to decrease the elevated possibility of death in COPD patients. For this rationale, medications are given in a stepwise manner (**Fig 2**). Short-acting bronchodilators must be inhaled to treat mild symptoms like exertional breathlessness. The addition of a long-acting muscarinic antagonists or bronchodilators is beneficial for patients who require repetitive inhalations each week. The patient's response and preferences determine the second-line medicine to use [15]. The G-protein coupled beta-2 receptor, which is primarily targeted by bronchodilators, relaxes the smooth muscle linings of the airways. They are metabolized in gut by cytochrome P-450 enzymes. Maximum percentage of drugs is eliminated in urine, and less than 20% is excreted in feces.

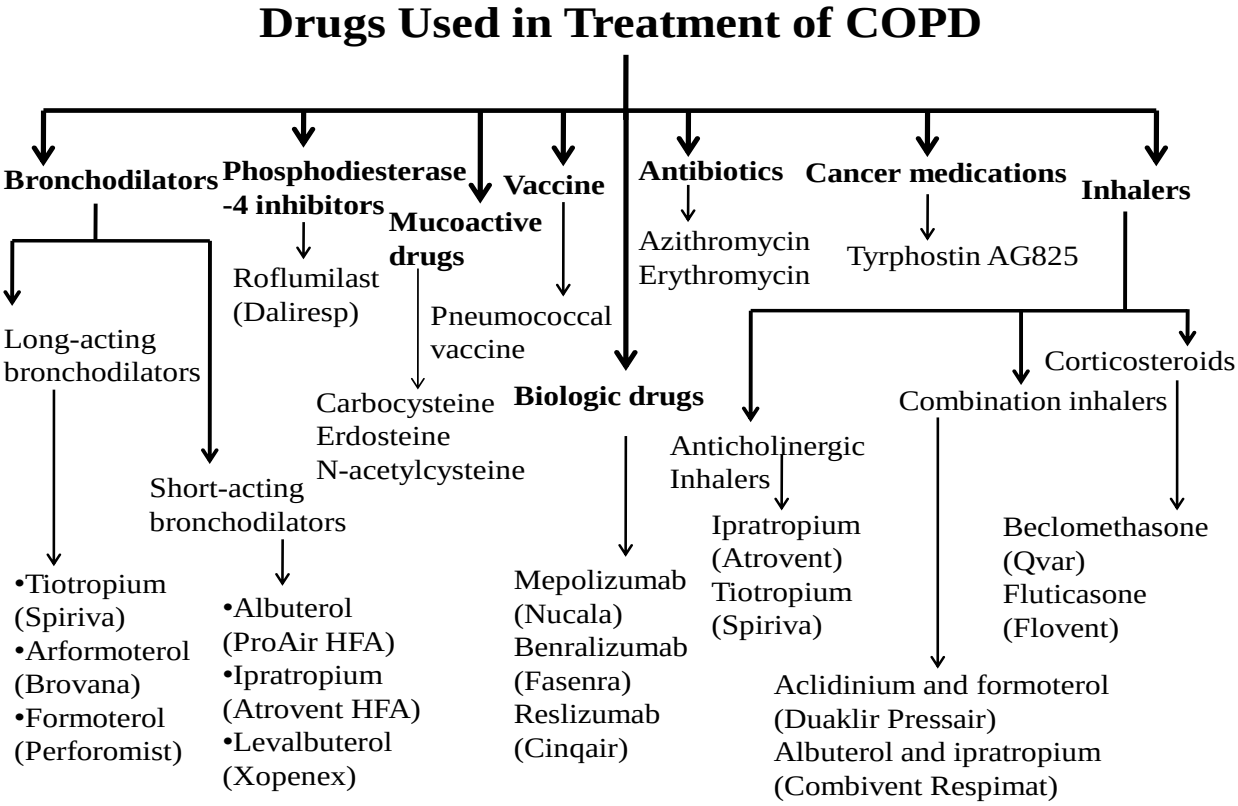

Fig 2: Drugs used in treatment of COPD

4.2 Combination therapy

Combination of inhaled corticosteroids/long acting bronchodilators therapy is advised in the management of COPD patients whose FEV1 (forced expiratory volume) is less than 50% predicted volume and for patients who have experienced many incidences of shortness of breath in the last 12 months [13]. Patients who are already receiving long-acting bronchodilator medication will go to "triple therapy". The accessibility of combined drugs (long acting bronchodilator, dual bronchodilators, and a long-acting muscarinic antagonist) in a single device has helped in using this prototype. In general, the combination is preferred than a single drug [16].

4.3 Antioxidant Therapies for COPD

4.3.1 Thiol Derivatives

Catalytic antioxidants, N-acetyl-L-cysteine (NAC), N-isobutyl cysteine (NIC), Nrf2 activators, N-acystelyn (NAL), and other substances decreased the burden of oxidative stress and inflammation in the lungs. They regulated the production of glutathione (GSH) along with the stimulation of NF-κB, which influenced the chromatin remodeling mechanisms, the redox system, and binding of transcription factor with the regulators of inflammatory mediator's genes. Thus, they helped in reducing the oxidative trauma [17]. Erdosteine, carbocysteine, fudosteine, porphyrins, procysteine, and spin traps are thiol compounds with advanced mucolytic capabilities that reduced the bacterial stickiness and inflammation related to COPD.

i. N-Acetyl-L-Cysteine (NAC)

N-acetyl-L-cysteine, or NAC, is the acetyl derivative of cysteine. It detoxified different inflammatory pathways by increasing glutathione levels. It undergoes deacetylation in digestive tract and produced cysteine that act as building blocks for glutathione fabrication. Dodd et al., showed that NAC increased the concentration of endogenous glutathione [18] and demonstrated that increased levels of cellular glutathione in lungs altered the cell's redox system by interacting with reactive oxidants. But Burgunder et al., opposed this and demonstrated that NAC converted cystine to cysteine [19]. In a COPD exacerbation model, Cazzola et al. verified that antioxidant and anti-inflammatory effects of NACs reduced the adverse effect of lipopolysaccharide's (LPS) [20].

NAC enhanced the lung function and mucociliary clearance by dislocating the cross linking and decreasing the viscosity and elasticity of mucus secretion. Lee et al. showed that NAC decreased lung allergies via controlling hypoxia-inducible factor-1 and activating NF-κB [21]. According to Passi et al., a double-blind, multicenter research found no improvement in lung function or mucus production in individuals with long-term chronic cough who were using NAC dosage inhalers [22].

ii. N-Acystelyn (NAL)

NAL is a lysine salt of NAC and used as alternatives to NAC. According to Antonicelli et al.'s research, NAL has thiol like antioxidant properties and acts as a mucolytic agent to reduce the oxidative stress and inflammatory response caused by ROS in both *vivo* and *in vitro* settings [23]. NAL enhanced the intracellular glutathione levels twice than NAC. Elborn et al showed that N-acystelyn (NAL) in aerosol form reduced mucus stiffness without any evident negative effects [24]. Therefore, NAL is more specific in targeting than NAC and in eradicating oxidative stress in chronic lung diseases.

iii. Carbocysteine

Lysine salt of S-Carboxymethyl cysteine (S-CMC-lys) is act as a prodrug that disintegrated in digestive tract and converted into active drug S-Carboxymethyl cysteine (S-CMC). According to Macci et al, it enhanced mucociliary transmission by decreasing the consistency of mucus [25]. It further decreased ROS levels in NCI-H292 cell line that encourage human neutrophil elastase (HNE) for causing hypersecretion of mucus. According to Yasuo et al., carbocysteine improved the survival of cell by stimulating the PI3K-AKT pathway and avoiding the cell damage/apoptosis brought on by H_2O_2 [26]. It has been reported that carbocysteine reduced the risk of bacterial infections in respiratory tract of COPD by preventing the pathogens' adhesion to cells. This report is supported by research of Cakan et al., which demonstrated that treatment with carbocysteine reduced the cohesion of Streptococcus pneumoniae with pharyngeal epithelial cells in both healthy volunteers and in patients of chronic bronchitis [27]. Wang et al., demonstrated that carbocysteine protected the human lung cancer cells against H_2O_2-induced cell damage by suppressing NF-κB and MAPK-$ERK_{1/2}$ signaling pathways [28]. Thus, the above-listed research has verified both anti-oxidant and anti-inflammatory potential of carbocysteine.

iv. Erdosteine

Erdosteine enhanced mucus clearance by rupturing the disulfide bonds of mucus glycoproteins and decreased sputum viscosity and elasticity due to its mucolytic potential. As an antibacterial agent, it prevented germs from adhering to cell surfaces. It worked as an anti-inflammatory agent by scavenging the free radicals and ROS [29]. Numerous clinical trials have confirmed the erdosteine's ability to prevent COPD exacerbations by salvaging ROS. Moretto et al., demonstrated that erdosteine in dose of 300 mg b.i.d. for 8 months and 300 mg twice for 7–10 days reduced exacerbation and hospitalization rates of COPD patients [30]. For 1 year, a 300 mg dose of ergosteine was proven to be helpful for 40 to 80 years aged group patients of COPD. Dal Negro et al confirmed its tremendous adhesive and anti-inflammatory potentials [31]. According to published research, erdosteine preserved the intensities of the cytokines IL-6 and IL-8 in the bronchial discharge of COPD patients while reducing the ROS production by activated macrophages due to cigarette smoke.

v. Fudosteine

Due to its anti-oxidant and mucolytic qualities, fudosteine is utilized to treat bronchial asthma, pulmonary emphysema, and COPD. Fudosteine have ability to donate cysteine amino acid and improved glutathione production. It has more bioavailability than NAC. Rhee et al demonstrated that fudosteine decreased the expression of MUC5AC gene and secretion of mucus and inhibited the key signaling molecules [32]. Osoata et al., demonstrated that fudosteine repressed the peroxynitrite-initiated oxidative stress by foraging the free radicals that are assumed to be responsible for the pathogenesis of COPD [33].

vi. Procysteine

Procysteine donates cysteine on disintegration and decreased the generation of IL-1 and TNF-α, which are necessary to augment macrophage activity. It has higher bioavailability than NAC. According to Hodge et al., Procysteine declined the ratios of glutathione-to-oxidized glutathione in lungs that augment the phagocytic action of macrophages [34].

4.3.2 Nrf2 Activating Drugs

The cytoplasm of healthy cells contains basic-leucine zipper transcription factor also known as nuclear factor erythroid 2-related factor (Nrf2). It acted as a master transcription factor and utilized the antioxidant response element (ARE) signaling pathway to regulate the appearance of different antioxidant genes like NAD(P)H dehydrogenase, thioredoxin reductase 1, heme-oxygenase, and superoxide dismutase 1 (SOD1) [35]. In oxidative and electrophilic stresses, Nrf2 switches into the nucleus and attached with antioxidant response element (ARE) of mark genes after detaching from its Kelch-like ECH-associated protein 1 (Keap1) and cytosolic inhibitory subunit [36]. It triggered the ARE-mediated Phase II detoxifying enzymes/genes and providing shield to the organism against oxidative and electrophilic stress [37]. Thus, Nrf2 is assumed as a crucial target that can lower the oxidative stress on the lungs. In COPD, Nrf2 activation reduced the influence of free radicals brought on by cigarette smoking while maintaining intracellular oxidant levels. Different Nrf2 activators are crucial in lowering oxidative stress are discussed below.

i. Sulforaphane

Sulforaphane is an organosulfur molecule that is mostly available in cruciferous vegetables including kale, cauliflower, and broccoli sprouts. It detoxified the ROS and unpaired radicals produced and ingested by the body [38]. Zeng et al demonstrated that sulforaphane inhibited the performance of TLR4 and MyD88 due to its anti-inflammatory potential in COPD [39]. Harvey *et al*. demonstrated that sulforaphane reticent the bacterial infection persuaded the exacerbation in COPD and reinstated bacteria detection and phagocytosis in alveolar macrophages (AMs) of patients by activating Nrf2 [40]. Yoon et al., demonstrated that sulforaphane activated Nrf2-reliant Phase 2 detoxification enzymes and prohibited the kidney impairment due to ROS induced oxidative stress [41]. Keum et al., observed that Nrf2 improved the performance of anti-oxidant enzymes by activating ARE [42].

ii. Curcumin

A yellow-colored antioxidant chemical with anti-inflammatory potential found in turmeric is curcumin. Mollazadeh et al., confirmed that curcumin concealed the pro-inflammatory cytokines that leads to its antiproliferative and anti-inflammatory effects [43]. Trujillo et al. and Safari et al. confirmed that curcumin accelerated the genes transcription that decreased the generation of reactive oxygen species and enhanced the antioxidant defensive mechanism [44-45]. Rushworth et al., observed that curcumin improved the activity of p38 phosphorylation and protein kinase C. It augmented the accessibility and performances of cellular anti-oxidant enzymes by conjugating ARE with Nrf2 transcription factor. Daily consumption of curcumin (100 mg/kg) prohibited the airspace reduction and augmented the macrophages and neutrophils inflammatory cells due to cigarette smoke. Thus, curcumin potentialy inhibited the elastase-driven pulmonary inflammation and emphysema in mice [46].

iii. Resveratrol

According to research by de Ligt et al., the phytoalexin resveratrol may trigger Sirtuin 1 either explicitly or implicitly by activating AMPK, which in turn stimulates PGC-1, a key regulator of mitochondrial metabolic processes and biosynthesis [47]. It is present in berries skin, peanuts, and red grapes. It provides protection from different stressors and destruction by exhibiting anti-inflammatory, anti-oxidant, and anti-carcinogenic properties. It activated Nrf2, which stimulated the production of nitric oxide by activating different detoxify enzymes like superoxide dismutase, glutathione peroxidase, heme-oxigenase-1, and catalase and protected the body against different stressors and damage [48]. Beijers et al., accounted that resveratrol consistently reduced oxidative stress and inflammation of lungs in experimental models of COPD. Thus, it improved both respiratory and skeletal muscle impairment in COPD [49]. Kode et al., illustrated that GSH and HO-1 levels enhanced in A549 cells during treatment with resveratrol by signaling Nrf2-ARE networks. It decreased the synthesis of Beclin1 protein and increasing the appearance of FoxO3a and SIRT1. It inhibited the autophagy in human bronchial epithelial cells *in- vitro* and in animals with COPD persuaded by cigarette smoke and LPS [50]. Li et al., found that resveratrol reduced the oxidative stress due to cigarette smoke in epithelial cells of human lung by SIRT1 nuclear migration of Nrf2 [51].

iv. Catechin

Polyphenols of green tea are usually known as catechins. Catechin is a natural phenolic flavonoid with antioxidant properties. Some examples of catechin are (-)-epicatechin (EC), (-)-epigallocatechin-3-gallate (EGCG), (-)-epicatechin-3-gallate (ECG), and (-)-epigallocatechin (EGC). Because of its extensive anti-inflammatory, antioxidant, and anti-fibrotic activities, the polyphenol EGCG produced from the green tea plant (Camellia sinensis) may also be helpful for the treatment of respiratory disorders [52]. Xanthine oxidase, mitochondrial succinoxidase, lipoxygenase, NADPH oxidase, COX-2, microsomal monooxygenase, etc. are pro-oxidant enzymes that produced superoxide anions. Yousefian et al., confirmed that the antioxidant potential of Catechin is due to its potential to chelate free transition metals like copper, iron and amplify the ROS production [53]. EGCG inhibited NF-κB activation by inhibiting release of pro-inflammatory cytokines in epithelial cells of airway due to cigarette smoke [54]. According to Shah et al's investigation on the protective effects of epicatechin produced from tea and cocoa plant against ischemic brain injury, HO-1 enzyme expression was raised by stimulating Nrf2 [55].

v. Terpenoids

Terpenoids (five carbon atoms) are also known as isoprenoids. They triggered the Nrf2 signaling pathway and diminished the damage caused by oxidative stress. Sussan et al beleaguered Nrf2 using triterpenoid CDDO imidazolide to appreciably decrease the alveolar destruction, pulmonary oxidative load, and cellular death brought on by smoking cigarettes [56]. Hirota et al demonstrated that in a mouse asthma model, limonene greatly decreased the concentration of several pro-inflammatory chemicals as well as airway fibrosis [57]. *In vivo* research employing an asthmatic rat model revealed that α-terpineol derivatives promoted airway smooth muscle relaxation and enhanced lung function. [58]. Chi et al demonstrated that borneol and terpineol can be utilized to treat asthma as they prohibited histamine-induced *in vitro* breathing problems in isolated guinea pig tracheal smooth muscles [59]. Kennedy-Feitosa et al., identified the saturated monoterpene eucalyptol as a potential anti-oxidant and anti-inflammatory option to cure COPD in mice [60]. A pentacyclic-triterpene derived from the plant Taraxacum officinale called taraxasterol is effectively combated the CS-induced lung inflammation in mice and in HBE cells by blocking the TLR4 receptor's trafficking to lipid rafts, which is generated by reactive oxygen species (ROS) [61].

vi. Quercetin

Red wine, berries, apples, Ginkgo biloba, onions, and other vegetables and fruits contain quercetin (3,3′,4′,5,7-pentahydroxy flavone), a phenolic molecule obtained from the flavonoid family. Due to its potential for antioxidant activity, quercetin converted into less reactive phenoxy radicals by interacting with reactive species [62]. Thus, they prevented the lipid peroxidation by counteracting with different reactive oxygen species. It inhibited different antioxidant enzymes, protein kinases, and activated the NF-κB pathway [63] that leads to inhibition of redox imbalance, expression of MMP9 and MMP12 [64].

4.3.3 Lipid peroxidation and protein carbonylation inhibitors/blockers

i. Edaravone (MC-186)

According to Kikuchi et al., edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) is a powerful lipid peroxidation determent and a potential scrounger of protein carbonyl and free-radical [65]. It reduced the intestinal ischemia/reperfusion persuade oxidative stress, lung damage, inflammation, and premature death in rats [66]. It is used to treat COPD because of its anti-inflammatory and antioxidant potential. It also improved the neurological function of patients and have applications in therapy of acute cerebral infarction [67-68]. Chen et al., demonstrated that edaravone have anti-necrosis, anti-apoptosis, and antioxidant potential [69]. Wang et al., had shown inhibitory efficacy of edaravone against lung damage in different ALI animal models [70].

ii. Lazaroids

Lazaroids (tirilazad mesylate), belongs to a class of glucocorticoid equivalents of methyl-prednisolone. They permeated in the hydrophobic sections of cell membrane in order to prevent the peroxidation of lipid membranes [12]. In different animal models of lung injury, lazaroids have been exhibited the function of protection [71]. According to Wang et al. lazaroids activated the alveolar macrophages to produce tumor necrosis factor and prohibited the production of free radicals in a model of lung damage brought on by smoking [72]. Further researches are required to determine effectiveness of lazaroids in COPD.

4.4 Enzyme Antioxidant

The primary use of enzyme-based anti-oxidants such catalase, superoxide dismutase (SOD), and glutathione peroxidase (GPx) is to eliminate reactive oxygen species created within the cells. These enzymes' expressions and capacities alter with oxidative stress. As a result, the use of enzyme mimics can aid in preserving the steadiness between anti-oxidant and oxidant systems. An enzyme imitated the usual function of the enzyme in its native form by having catalytic activity.

4.4.1 SOD (Superoxide Dismutase) Mimetics

Superoxide dismutase is located in the lungs as an extracellular superoxide. Lungs exposed more to free radicals than other organs. It captured superoxide anion and shielded the lung from oxidative stress-related harm. Mimicking enzymes are categorized in three classes. Numerous manganese-based macrocyclic ligands, such as M40414 and M40401, are part of the foremost class of SOD enzyme mimics [73]. Manganese metalloporphyrins like AEOL-10113 and AEOL-10150 are part of the subsequent class [74]. Salens that have superoxide dismutase and catalase activity make up the third class. They could eliminate a large number of unpaired radicals like hydrogen peroxide, peroxynitrite radicals, and superoxide anion. M40419 dramatically reduced the levels of oxidative stress indicators found in lung tissue of animal model. AEOL-10150 reduced the synthesis of peroxynitrite, lipid peroxidation and cigarette smoke-induced inflammatory response. According to Yao et al., superoxide dismutase prevented tobacco smoke and elastase-induced lung fibrosis in mice by reducing ECM division and altering elastin fragments formed due to oxidative burden [75]. Tollefson et al., demonstrated that SOD_3 helped in declining the oxidative burden in macrophages of mouse [76]. Therefore, the development of enzyme mimics is thought to be a beneficial therapeutic approach in the therapy of COPD and emphysema.

4.4.2 Glutathione Peroxidase Mimetics

Ebselen compounds are potent antioxidants because they counteracted the effects of the peroxynitrite radical. These are selenium-based compounds that imitating the functions of glutathione peroxidase. It prohibited the LPS-induced soreness and enrollment of inflammatory cells like neutrophils by restraining the TNF-α and IL-1β. These experiments showed that the enzyme mimetic is proved valuable in reducing oxidative burden associated with lung inflammation [76].

4.4.3 Enzymatic Redox sensors: Thioredoxin

Redox effector factor-1 (Ref-1) and thioredoxin (Trx) are the redox sensors of family oxidoreductase. It improved the cell functions by decreasing oxidative stress directly due to its antioxidant potential and indirectly by interacting proteins with key signal transduction molecules [77]. Thioredoxin joined with the apoptosis signal regulating kinase and hepatopoietin proteins during oxidative stress [78]. It induced transcriptional activation by suppressing the thiol group in p65/NF-κB subunit. Souza et al demonstrated that MOL-294 suppressed thioredoxin leads to blockage of nuclear stimulation of NF-κB and AP-1-dependent transcription, annihilation of neutrophil influx and production of TNF-α in an animal model [79]. Tanabe et al., demonstrated that thioredoxin prevented cigarette smoke-induced emphysema by its anti-chemotactic effects produced due to its anti-inflammatory and anti-oxidative characteristics [80]. The level of 4HNE is augmented during oxidative stress in lungs of COPD and in serum of AECOPD patients [81]. 4HNE attached with the active-sites of Trx1 and cytosolic TrxR to produce its cytotoxic effects (TrxR1) [82-83].

4.4.4 Spin traps and iNOS inhibitors

Spin traps formed stable end products by quenching the free radicals. Nitrone- or nitroxide-nuclei and their derivatives are typically found in spin traps. Initially spin traps generated toxic hydroxyl radicals due to their small half lives. This issue has been resolved by adding electron withdrawing molecules to the pyrroline ring [84]. Due to their potent antioxidant effects, isoindole- and azulenyl-based nitrones like STANZ reduced lipid peroxidation. At the site of inflammation, compound BN 80933 (a-phenyl-N-tert-butyl) is converted into the stable forms on reaction with free radicals [85]. Phenyl-base nitrone spin trap (PBN) derivative, like PBN-2, 4, disulfonate (NXY-059) has been reported to be useful in a number of experimental mock-ups of pulmonary diseases (http://www.nitrone.com/). Recent studies revealed that a number of pharmacological inhibitors, including G-nitro-L-arginine-methyl ester (L-NAME) and [N (6)-(1-iminoethyl)-L-lysine (L-NIL) reduced iNOS and thereby eased emphysema in different animal models [86]. Therefore, targeted suppression of iNOS and substitution with other antioxidants may offer a treatment plan for COPD.

4.5 Nanocarriers

Different nanocarriers can be manufactured with different materials like synthetic and natural polymers, organic and inorganic compounds made of proteins, metals, and lipids, for the treatment of chronic lung illnesses. Nanoparticles can be divided into various classes on the basis of their constituents and distinguishing characteristics, like solid-lipid nanoparticles, micelles, polymeric nanoparticles, dendrimers, liposomes, inorganic nanoparticles and protein-based nanoparticles (**Fig 3**) [87].

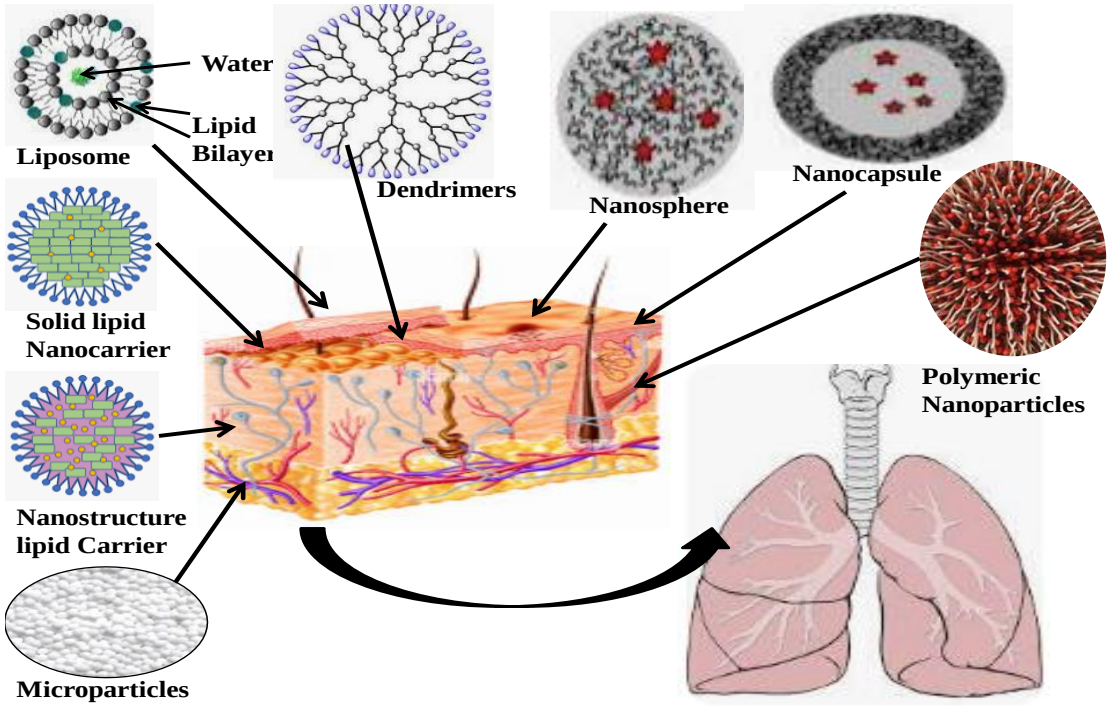

Fig 3: Different nanocarriers for targeting drugs in lungs.

4.5.1 Liposomes

Liposomes are lipid-based spherical medication carriers having bilayer lipid membrane. Polymers like polyethylene glycol (PEG) and chitosan are typically used to modify their outer surface [88]. By reducing cellular uptake by the phagocytic system, these coatings lengthened the duration that the liposomes spent in the bloodstream. STEALTH technology enabled to encapsulate a wide variety of active ingredients in liposomal carriers to increase the targeting efficiency and activity. STEALTH liposomes are the common name for these liposomes. The composition of the liposomal membrane can be modified to create neutral, anionic, and cationic liposomes [89-90].

Liposomes are prepared different materials that are compatible with pulmonary tissue and assisted the targeted intracellular delivery of drug via merging with the membrane of plasma, phagocytosis, and receptor-triggered endocytosis [91]. Liposomes are extensively used for targeted delivery of nucleic acids (DNA/RNA), vitamins and drugs in the form of aerosol [92]. Modification of curcumin-loaded liposomes provided the protection to the entrap molecule and increased their efficacy in chronic inflammatory conditions. They improved the performance of nebulizer and reduced lung damage due to oxidants. Manconi et al observed that the synergic effect of hyaluronan and curcumin subsequently enhanced the metabolic activity of cells [93]. The various benefits shown by liposomes in dry powder form with breathing devices for lungs are as follow. Firstly they do not aggregate after aerosolization, secondly retained drug payload and their size during spray. They accumulated in lungs and retained there for a longer duration. Then, they penetrated into the lung cells and depicted the sustained liberation of active content [94]. Li et al. developed a liposomal dexamethasone administration technique in conjunction with an antibody to specifically target surfactant protein [95]. They demonstrated that liposomal steroids had higher therapeutic effectiveness and lesser side effects than free dexamethasone sodium phosphate. Cipolla et al encapsulated ciprofloxacin nanocrystals in liposomal formulations and converted them in freeze-dried aerosolized form [96]. They demonstrated that these formulations were remained stable for a long duration after nebulization. De Leo prepared small unilamellar surface modified liposomes to evaluate the penetrating efficacy of these vesicles in the amelioration of persistent respiratory illnesses by testing pathological mucus model of COPD [97].

4.5.2 Nanoparticles

Nanoparticles are used as novel carriers for the targeted administration of medications in lungs [98]. They focused mainly on the pulmonary airway's endothelial cells' like platelet endothelial cell and receptors of intracellular cell attachment molecule. Nanoparticles reduced the oxidative stress of respiratory system by targeting different drugs like SOD, NADPH oxidase inhibitors, and CAT [99]. The relevant researches that focused on COPD therapy with nanoformulations were summarized in Table 1.

i. Solid Lipid Nanoparticles

Cholesterol and phosphatidylcholine are used to prepare lipid-based nanoparticles as they are biocompatible. These nanocarriers can encapsulate extensive assortment of drugs in inner and the outer lipid layer to encourage cellular uptake. Dipalmitoyl phosphatidyl ethanolamine-methoxy (polyethene glycol) (DPPE-PEG) and Dipalmitoyl phosphatidy lcholine (DPPC) based nanocarriers are utilized to deliver drugs in respiratory tract. Meenach et al prepared a micro/nanoparticle system to deliver anti-cancer drug paclitaxel in lungs by using dipalmitoyl phosphatidy lethanolamine PEG (DPPE-PEG) and DPPC/DPPE-PEG dipalmitoyl phosphatidylcholine (DPPC) [100]. Castellani et al. prepared SLNs based drug delivery system by using a melt-emulsion technique to trap proanthocyanidins and demonstrated that they reduced oxidative stress by decreasing ROS generation [101].

ii. Lipid Hybrid Polymer Nanoparticles

The most recent innovation in nanocarriers is nanostructured lipid carriers (NLC). For example, Thanki et al synthesized LPNs i.e. lipidoid-modified nanoparticles with lipidoid and PLGA and showed that they had substantial gene hushing effects. [102]. Akinc et al recommended lipidoid-modified LPNs as a hopeful prospect to ensure the proficient and secure intracellular delivery of siRNA in chronic pulmonary disease [103]. Wang et al effectively trapped Poly (lactic-co-glycolic acid) in lipid hybrid nanoparticles composed of phosphatidylcholine (PC) for its targeted delivery in lungs [104]. Chikuma et al encapsulated a cationic lipid (DOTAP) envelope that attached the pHDAC2 and Mn-porphyrin dimer in PLGA core in LPNs and suggested that these vesicles eliminated ROS and revealed a considerable augmentation in intracellular HDAC2 expression levels [105]. Recently, the effective treatment of chronic inflammatory lung disorders has been achieved by using nanoparticles that have been loaded with antibiotics, anti-cancer medications, antioxidant agents, and anti-asthmatic medications.

Type	Nanocarriers Composition	Drug	Method of Preparation	Mode of Action	Ref
Liposomes					
Liposomes	Chitosan, hyaluronan, phospholipids	Curcumin	Sonication, stirring	Act by suppressing the generation of COX-2, IL-8, 4,5 and NF-κB activation	[93]
	Phospholipid and cholesterol	NAC	Reverse phase evapo-ration and spray drying	Reduce sputum viscosity in both COPD and cystic fibrosis to make it easier to remove lung secretions	[106]
	DPPC	a-Tocopherol	Solvent evaporation method	Reduce the influx of cells, acute inflammation, and collagen production in lung tissue.	[107]
Dendrimers					
Dendrimers	TEE modified PAMAM dendrimers	siRNA	Vortex	Target lung alveolar epithelial A549 cells and mute genes	[108]

	PAMAM dendrimer	TNF-α siRNA	Vortex	Gene silence (targeted TNF-α)	[109]
Nanoparticles					
Solid lipid nanoparticle	Lipid and surfactant	Proanthocyanidins	Melt-emulsion method	Reduce ROS production	[110]
	Lipid	Carvacrol	Fusion-emulsification method	Reduce level of malondialdehyde to reduce the respiratory harm, and diminish the histopathological alteration	[111]
Polymer hybrid nanoparticles	PLGA and DOTAP	siRNA	DESE	Gene silence (targeted TNF-α)	[102]
	PLGA and DOTAP	pHDAC2, MnPD	Modified solvent displacement method	Decreased glucocorticoid defence and ROS levels	[105]
Biodegradable nanoparticles	Poly(ε-caprolactone)	Lipoic acid	Interfacial polymer deposition	Protection against lipid peroxidation	[112]
	Polyoxalate	HBA	Conventional single emulsion method	Salvage H2O2, decrease iNOS, COX-2, and (IL)-1β expression	[113]
Polymeric nanoparticles	PHEA-PLA-PEG2000	FP	HPH (freeze drying)	Promote drugs mucus layer absorption, decrease survivin expression	[114]
	PVP; PVA or dextran	Curcumin	Solvent and antisolvent precipitation method	Time-dependent attenuate in LPS-induced inflammation of alveolar macrophages	[115]
	PGA-co-PDL, cationic lipid DOTAP	microRNAs	Single emulsion solvent evaporation method	Reduce the expression of IRAK1 and the activity of the IL-8 promoter.	[116]
	PLGA, calcium phosphate, chitosan or PEI	siRNA, pDNA, FITC-BSA	Modified the rapid precipitation method (freeze drying)	Amplify the encapsulation of siRNA or DNA and pervade through the cell membrane	[117]
	PLGA, calcium phosphate, polyethylenimine	siRNA	Modified the rapid precipitation method (freeze drying)	Suppress the expression of IFN-γ, CCL-2 and IP-10 to decrease the lungs inflammation	
Multifunctional nanomaterials	Fibroin	Sulforaphane, CeNPs and PEI passivated CDs	Modified solvent displacement method	Against oxidative stress and imaging	[118]
Nanocrystals	Pluronic F68 or lecithin	Budesonide	Wet-milling technique	It activated glucocorticoid receptors (GR) in the cytoplasm of bronchial cells, causing the budesonide-GR complex to connect with HDCA2 and CBP (HAT) in the nucleus of the bronchi.	[119]
Inorganic nanoparticles	Gold nanoparticles	Au	NaBH4 reduction method	Quickly bind with alveolar epithelium	[120]
	Ferrous and ferric chlorides	Antibody conjugates	Controlled precipitation approach	Facilitate endothelial delivery of active contents and provide protection against proteolysis	[121]
	Cerium oxide (IV) nanoparticles	SOD and CAT		Against ROS	[122]
	Al_2O_3 NPs	Al_2O_3	(Purchased from Plasmachem Gmb)	PTPN6 and STAT3 phosphorylation are repressed. Restoring PTPN6 production or using a STAT3 inhibitor to prevent inflammation and apoptotic in the lungs	[123]

Table 1: Different Nanocarriers used for targeted delivery in COPD

iii. Inorganic nanoparticles

Inorganic nanoparticles are made of silver and gold or inorganic materials like carbon, silicon oxide, iron oxide, and calcium phosphate. Targeted delivery, wide availability, good biocompatibility, and affluent functionality are the versatile properties of inorganic nanoparticles that made them suitable for pulmonary delivery. They can therefore be evaluated as potential COPD nanocarriers. For instance, gold nanoparticles are used to target drug in epithelial cells during COPD [120]; cationic nanoparticles are used for gene delivery by binding with anionic DNA/RNA [124]. Gil et al conjugated antioxidative enzymes with inorganic cerium oxide (IV) nanoparticles to capture nitrogen and oxygen radicals and recommended that antioxidative enzymes and the nanocarriers provide a synergetic anti-inflammatory effect by targeting endothelial cells [125]. Fytianos et al prepared fluorescently coated gold nanoparticles and functionalized their surface with DC-SIGN antibody [126]. Protein-based drug delivery systems are used to amend the exterior of inorganic nanoparticles in order to minimize the problems associated with these nanoparticles, such as immunogenicity, less biological compatibility, and low biological degradation. One such example is the encapsulation of cerium oxide nanoparticles into albumin nanoparticles by Bhushan et al [127]. Additionally, Murlidharan et al., productively prepared nanoparticles encapsulated Nrf2 activator like dimethyl fumarate in dry powders form inhalable for the targeted delivery in pulmonary inflammation [128].

iv. Polymeric nanoparticles

The macromolecules known as polymers are prepared by repeating monomers. Various types of polymers can be combined with active components like drugs, nucleic acids, targeting moieties, etc. directly or via fillers with various designs to produce a range of polymeric drug delivery systems. The most widely used natural polymers are albumin, HA, chitosan, and gelatin, while the most popular synthetic polymers are PEG, PLA, PVA, and copolymers like PLGA [129]. Vij et al prepared a multipurpose polymeric vesicle to co-encapsulate theophylline and prednisolone as a combined regimen for relief during chronic lung illnesses [130]. Nanoparticles encapsulated biodegradable hydroxybenzyl alcohol-incorporated polyoxalate (HPOX) reduced the oxidative stress and used to cure inflammatory illnesses of the airways. Intranasal HPOX administration has shown allergic inflammation and significantly decreased iNOS expression [131]. The dilapidation products of PLGA like glycolic acid and lactic acid were accumulated in pathways of respiratory tract and caused alteration in pH [132]. Therefore, before implementing a polymeric drug delivery approach, it is strongly encouraged to evaluate the rate of polymer breakdown and long-term safety.

4.5.3 Dendrimers

Dendrimers are repeated branched structure of size 4 to 20 nm that can be used as hauler to deliver a drug. They have applications in the efficient delivery of numerous drugs, steroids and antibiotics. Vigorous penetration of dendrimers in blood restricted their retention in lungs. Ryan et al. prepared PEGylated dendrimers and investigated their ability to retain in lungs and to discharge the drug in sustained manner [133]. Kaminskis et al encapsulated doxorubicin conjugated with 56 kDa PEGlyated poly-lysine in dendrimers to examine their anti-cancer potential and demonstrated that they are quickly evacuated from the respiratory tract after introducing via intra-tracheal route [134]. Zhong et al., demonstrated the cellular and systemic biodistribution of PAMAM dendrimers [135]. Dendrimers can be used to deliver drug potentially by inhalation. Dendrimers having charge on its surface were effectively used for the transport of genetic material. Khan et al., prepared dendrimer using alkyl chains of increasing length instead of free amine and evaluated its ability for the targeted delivery of siRNA [136]. Bohr et al., prepared and recommended that pyrrolidinium dendrimiplexes had higher cellular incorporation and *in vitro* TNF silencing effectiveness than morpholinium-containing dendrimiplexes [137].

4.5.4 Nanospheres

Nanospheres are nanocarriers of amorphous or crystalline nature with size up to 10-200 nm mainly designed to deliver gene and drugs. They protected the active molecule against enzymatic and chemical deterioration. Some examples of nanospheres include nanospheres made of albumin, gelatin, polylactic acid and dextran. Pitard et al., synthesized a nanosphere employing ethylenediamine as central moiety and attached four polyethylene oxide/polypropylene oxide units to it, to deliver chemotherapeutic agents. These nanospheres have positive charges so coupled easily with nucleic acids/plasmids [138]. Jiang et al., also created chitosan nanospheres loaded with paclitaxel and observed their favorable bioavailability and prolonged release characteristics. They showed that these nanospheres prevented A549 cells from proliferating and increased apoptosis [139].

4.5.5 Nano-Theranostics for Chronic Obstructive Lung Diseases

A new age in lung care will be escorted by nano-theranostics. It prepared nanocarriers for multifunctional airways that can do both diagnostic and therapeutic tasks. These nanocarriers will act as suitable delivery system for therapeutic molecules and be joined with imaging components at the same time to enable several activities like cell therapy, targeting, and ultra-sensitive imaging. As a result, it assisted in resolving issues that came up during the management and in increasing the endurance rates of COPD patients [130]. Numerous multifunctional inorganic nanoparticles, including gold NPs, have applications in therapy of lung tumors, either to enhance the optical ability or for photo thermal chemotherapy. This is exemplified by the use of magnetic iron oxide nanoparticles to encapsulate drug and silica shell to transport MRI contrast agent and hydrophobic drug simultaneously, which facilitated diagnostics and treatments in a solitary device. In spite of recent advancements, COPD required the development of multifunctional nanosystems. Theranostic methods designed for cancer have restricted uses in chronic airway inflammation because of their hazardous effects and constant inflammation. Al-Jamal and Kostarelos used liposomes in fabrication of theranostic hybrids to enclose quantum dots and multiple drugs simultaneously [140].

Multifunctional polymeric vesicles are being produced by combining molecular probes with two synthetic polymers, for targeted administration of drugs like prednisolone, corticosteroids, and bronchodilators like theophylline in the management of chronic fibrosis and chronic lung ailments. These probe- and medication-loaded nanocarriers are employed as a theranostic system for the treatment of chronic lungs illness. It has been assumed that positively charged nanoformulations containing polymeric steroids were accumulated with more privileged at the location of airway irritation than free steroids. Monument et al., targeted ketofin fumarate (mast cell stabilizer) in form of dry powder aerosols to the lungs of rat by adopting liposomes as the nanocarriers [141].

The two most extensive techniques utilized to assess lung cancer in people at the moment are positron emission tomography (PET/CT) and single photon emission computed tomography (SPECT/CT). These entailed that the positrons released by radio labeled tracers have been collected near the targeted tissue. One of these tracers is the radioactive marker fluorine-18-fluorodeoxyglucose (FDG). The potential of FDG is to accrue at inflammatory site like activated macrophages, making it a mandatory task for inflammatory lung illnesses. Thus, the innovative molecular probes are being developed that can identify inflammation, bacteria and viruses, and cell apoptosis. They can be beneficial to recognize the cellular mechanisms influenced in the aetiology of progressive obstructive pulmonary illnesses.

4.6 Microformulations

Recently microformulations have also become more and more popular owing to their particle size, excellent drug loading and entrapment efficiencies, their sustained-release characteristics, and clinical benefits. Pulmonary delivery of drugs in form of microparticle inhalers has gain popularity to produce local and systemic effects of medications. Depending on the particle size, three different processes like gravitational sedimentation, inertial impaction, and brownian diffusion lead to the deposition of microparticles in the lungs. Particles with size less than 1 μm may be breathed back while the particles that exceed 10 μm are appropriate for accumulation in the oropharynx. Thus, microparticles with an assortment of 1 to 5 μm are idyllic for attaining efficient lung deposition. According to Xu et al., particles with aerodynamic dimensions of 1 and 5 μm are slowly accumulated in the pulmonary vessels and blocked airways [142]. Other properties that can manipulate aerosol performance include particle shape, density, polymorphism,

crystallinity, surface roughness and inter-particulate forces [143]. Table 2 summarizes pertinent studies that focused on microparticles to reduce oxidative stress.

4.7 Gene Therapy for COPD

Along with anti-inflammatory medicines and antioxidant therapy, gene therapy is an additional hopeful method to treat chronic obstructive pulmonary disorders. The initial step in the management of COPD is to identify the problematic gene. Then, design the vector and targeted delivery. For the management of pulmonary illness, adenoviral vector-based gene therapy has been measured as a preferable approach [158]. Cationic liposomes were also used for gene delivery in lungs. Bronchial cells have showed improved cellular uptake of liposomes that have been coupled with cell penetrating peptides. According to Swaminathan and Ehrhardt gene therapy has shown promising outcomes in treating adenovirus-induced CF in clinical trials and it may be a successful strategy for curing COPD [159].

Viral liposome complexes loaded with α1 anti-trypsin (AAT) gene, on i.v. administration in mice formed considerable amount of AAT in serum samples up to one month. Adeno-associated vector (AAV) is the other potential approach to deliver AAT transgene with less toxicity, prolonged effect and a high degree of transgene expression. Al-Jamal et al., developed genoplasty as a new technique for location-specific repair of solitary nucleotides in chromosomes using RNA/DNA oligonucleotides [160].

Type	Drug	Method of preparation	Mode of action	Ref
Porous microparticles	Budesonide	Modified single emulsion (O/W) solvent evaporation freeze drying	It activated glucocorticoid receptors (GR) in the cytoplasm of bronchial cells, causing the budesonide-GR complex to connect with HDCA2 and CBP (HAT) in the nucleus of the bronchi.	[144]
	Dexamethasone	Double emulsion method freeze drying	Salvage hydrogen peroxide, reduced the oxidative strain	[112]
Microscale dry powder	Budesonide or Salbutamol sulphate	(1) Jet milling (2) Spray-drying	Short acting β agonist, synthetic glucocorticoid	[145]
	Sodium ascorbyl phosphate	co-spray dried	Antioxidant, wound healing and anti-inflammatory properties	[146]
	Dimethyl fumarate	Co-spray dried	Nrf2 activator	[147]
	Fluticasone propionate, and Mometasone furoate	(1) Jet milling (2) Wet polishing	Long-acting β2-agonists	[148]
	Resveratrol	Spray-drying	Salvage activity of DPPH free radicals	[149]
	Resveratrol	Spray-drying	Significantly reduced the expression of IL-8 TGF-β1 and	
Clinical study	Ribavirin –PRINT –CFI	Non-wetting Templates (PRINT) technology	Act by inhibiting the key respiratory viruses like HRV, RSV, and IFV that leads to acute exacerbations in COPD	[150]
	Ribavirin-97 PRINT-IP	Non-wetting Templates (PRINT) technology		
Mucoadhesive solid lipid microparticles	Salmeterol xinafoate	High-pressure homogenization (freeze drying)	Long-acting β2 agonist	[151]
	Fluticasone propionate	Ethanolic precipitation technique (freeze drying)	ERK1/2 pathway activation	[152]
Nanocomposite microparticles	Budesonide	(1) High-energy wet media milling; (2) Spray drying	Anti-inflammatory activity	[153]
	MicroRNA	(1) Oil in water (o/w) single emulsion method; (2) Spray-drying	Genes silence of IRAK1 and TRAF6	[154]
	siRNA	(1) Double emulsion solvent evaporation method (2) Spray-drying	Dispersed microembedded LPNs had preserved physicochemical characteristics as well as in vitro siRNA release profile and gene silencing	[155]
	Apigenin	(1) Modified nanoparticle albumin-bound technology (2) Spray drying	It increased the SIRT1 level and reduced H_2O_2-induced senescence in lung diseases	[156-157]

Table 2: Different microparticles used in treatment of COPD

4.8 Stem Cell Therapy for COPD

Recent developments in the study of bone marrow mesenchymal stem cells (BM-MSCs) have led to a unique method for treating chronic respiratory disorders like COPD. In order to cure COPD, MSC transplantation entails the control of inflammation, protease/anti-protease balance, oxidative stress, and apoptosis [161]. The therapeutic regimen for MSC therapy is still not apparent, and further research is required to identify the right dosage, delivery method, and infusion rate. Additionally, there is a low degree of graft integration in the host organs and a low probability of survival [162]. Therefore, novel strategies must be established to improve the mortality rate of MSCs in host organs. Despite these challenges, MSC therapy is one of the effective ways to treat COPD.

5. Conclusion and future directions

The aetiology of COPD cannot yet be fully cured by any therapy. The development of nanotechnology has given opportunities for improvement in the anti-oxidant pharmaceutical medicines that are now used to treat COPD. The effectiveness and toxicity of an extensive variety of medications can be increased and decreased by using different nano- and microcarriers. Using nano- and micro-carriers and their alteration in surfaces, new therapeutic techniques have been developed to cure different chronic lung illnesses. Smart multifunctional drug carriers can be created with the

help of targeting ligands. Before we can completely utilize this technology's clinical potential, it must be fully developed and any obstacles must be removed. When converting "smart technology" into a clinical application, the cost-benefit ratio needs to be considered. A few examples include the demand and discovery of several targeting ligands as well as knowledge of the harmful effects of nanoparticles and their impact on immunity. Novel nano- and micro-materials are required to be fabricated that demonstrated pulmonary evacuation pathways after being accumulated in respiratory tract. Conjugation of nanotechnology with gene and stem cell treatment techniques can provide excellent scope for the creation of successful therapeutic strategies for the management of COPD and other chronic respiratory diseases.

6. Acknowledgments
None

7. Competing Interests
None

8. References

1. van Eeden SF, Sin DD. Oxidative stress in chronic obstructive pulmonary disease: a lung and systemic process. Can Respir J. 2013; 20: 27-29. doi: 10.1155/2013/509130
2. Passi M, Shahid S, Chockalingam S, Sundar IK, Packirisamy G. Conventional and Nanotechnology Based Approaches to Combat Chronic Obstructive Pulmonary Disease: Implications for Chronic Airway Diseases. Int J Nanomedicine. 2020; 15: 3803-3826. doi: 10.2147/IJN.S242516
3. Silva-Palacios A, Ostolga-Chavarría M, Sánchez-Garibay C, et al. Sulforaphane protects from myocardial ischemia-reperfusion damage through the balanced activation of Nrf2/AhR. Free Radic Biol Med. 2019;143:331–340. doi: 10.1016/j.freeradbiomed.2019.08.012
4. Saxena J, Bisen M, Misra A, Srivastava VK, Kaushik S, Siddiqui AJ, Mishra N, Singh A, Jyoti A. Targeting COPD with PLGA-Based Nanoparticles: Current Status and Prospects. Biomed Res Int. 2022 Mar 11;2022:5058121. doi: 10.1155/2022/5058121.
5. Brusselle GG, Joos GF, Bracke KR, "New insights into the immunology of chronic obstructive pulmonary disease," The Lancet, 2011; vol. 378, no. 9795, pp. 1015-1026,.
6. Barrecheguren M, Esquinas C, and Miravitlles M. The asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS). Curr Opin Pulm Med. 2015; 21(1): 74-79.
7. Taylor AE, Finney-Hayward TK, Quint JK, Thomas CM, Tudhope SJ, Wedzicha JA, Barnes PJ, Donnelly LE. Defective macrophage phagocytosis of bacteria in COPD. Eur Respir J. 2010; 35(5): 1039-1047.
8. Donnelly LE, Barnes PJ. Defective phagocytosis in airways disease. chest. 2012; 141(4): 1055-1062.
9. Kirkham PA, Barnes PJ. Oxidative stress in COPD. Chest. 2013; 144(1): 266-273.
10. Nakamaru Y, Vuppusetty C, Wada H, Milne JC, Ito M, Rossios C, Elliot M, Hogg J, Kharitonov S, Goto H, Bemis JE. A protein deacetylase SIRT1 is a negative regulator of metalloproteinase-9. The FASEB J. 2009; 23(9): 2810-2819.
11. Hara H, Araya J, Ito S, Kobayashi K, Takasaka N, Yoshii Y, Wakui H, Kojima J, Shimizu K, Numata T, Kawaishi M. Mitochondrial fragmentation in cigarette smoke-induced bronchial epithelial cell senescence. Am J Physiol Lung Cell Mol Physiol. 2013; 305(10): L737-L746.
12. Tanner L, Single AB. Animal models reflecting chronic obstructive pulmonary disease and related respiratory disorders: translating pre-clinical data into clinical relevance. J Innate Immun. 2020; 12(3): 203-225.
13. Jenkins C. Drugs for chronic obstructive pulmonary disease. Aust Prescr 2017; 40: 15-19. http://dx.doi.org/10.18773/ austprescr.2017.003.
14. McDonough M. Update on medicines for smoking cessation. Aust Prescr 2015; 38: 106-111. http://dx.doi.org/10.18773/ austprescr.2015.038
15. Bateman ED, Ferguson GT, Barnes N, Gallagher N, Green Y, Henley M, et al. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. Eur Respir J 2013; 42: 1484-1494. http://dx.doi.org/10.1183/09031936.00200212.
16. Decramer M, Anzueto A, Kerwin E, Kaelin T, Richard N, Crater G, et al. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. Lancet Respir Med 2014; 2: 472-486. http://dx.doi.org/10.1016/S2213-2600(14)70065-7
17. Rahman I, Macnee W. Antioxidant pharmacological therapies for COPD. Curr Opin Pharmacol. 2012; 12: 256-265.
18. Dodd S, Dean O, Copolov DL, Malhi GS, Berk M. N –acetylcysteine for antioxidant therapy: pharmacology and clinical utility. Expert Opin Biol Ther. 2008; 8: 1955-1962. doi:10.1517/147282 20802517901.
19. Burgunder JM, Varriale A, Lauterburg BH. Effect of N-acetylcysteine on plasma cysteine and glutathione following paracetamol administration. Eur J Clin Pharmacol. 1989; 36: 127-131. doi: 10.1007/BF00609183.
20. Cazzola M, Calzetta L, Facciolo F, Rogliani P, Matera MG. Pharmacological investigation on the anti-oxidant and anti-inflammatory activity of N-acetylcysteine in an ex vivo model of COPD exacerbation. Respir Res. 2017; 18: 26. doi: 10.1186/s12931-016-0500-y.

21. Lee KS, Kim SR, Park HS, et al. A novel thiol compound, N-acetylcysteine amide, attenuates allergic airway disease by regulating activation of NF-κB and hypoxia-inducible factor-1α. Exp Mol Med. 2007; 39: 756-768. doi: 10.1038/emm.2007.82.
22. Passi M, Shahid S, Chockalingam S, Sundar IK, Packirisamy G. Conventional and Nanotechnology Based Approaches to Combat Chronic Obstructive Pulmonary Disease: Implications for Chronic Airway Diseases. Int J Nanomedicine. 2020; 15: 3803-3826. doi: 10.2147/IJN.S242516.
23. Antonicelli F, Brown D, Parmentier M, et al. Regulation of LPS-mediated inflammation in vivo and in vitro by the thiol antioxidant Nacystelyn. Am J Physiol Cell Mol Physiol. 2004; 286: L1319-L1327. doi: 10.1152/ajplung.00329.2003.
24. Elborn JS, Bell SC, Madge SL, et al. Report of the European Respiratory Society/European Cystic Fibrosis Society task force on the care of adults with cystic fibrosis. Eur Respir J. 2016; 47: 420-428. doi: 10.1183/13993003.00592-2015.
25. Maccio A, Madeddu C, Panzone F, Mantovani G. Carbocysteine: clinical experience and new perspectives in the treatment of chronic inflammatory diseases. Expert Opin Pharmacother. 2009; 10: 693-703. doi: 10.1517/14656560902758343.
26. Yasuo M, Fujimoto K, Imamura H, et al. l-Carbocisteine reduces neutrophil elastase-induced mucin production. Respir Physiol Neurobiol. 2009; 167: 214-216. doi: 10.1016/j.resp.2009.04.016.
27. Cakan G, Turkoz M, Turan T, Ahmed K, Nagatake T. S-carboxymethylcysteine inhibits the attachment of Streptococcus pneumoniae to human pharyngeal epithelial cells. Microb Pathog. 2003; 34: 261-265.
28. Wang W, Zheng JP, Zhu SX, Guan WJ, Chen M, Zhong NS. Carbocisteine attenuates hydrogen peroxide-induced inflammatory injury in A549 cells via NF-κB and ERK1/2 MAPK pathways. Int Immunopharmacol. 2015a; 24: 306-313. doi: 10.1016/j.intimp.2014.12.018
29. Moretti M, Fagnani S. Erdosteine reduces inflammation and time to first exacerbation post discharge in hospitalized patients with AECOPD. Int J Chron Obstruct Pulmon Dis. 2015; 10: 2319-2325. doi: 10.2147/COPD.S87091.
30. Moretto N, Facchinetti F, Southworth T, Civelli M, Singh D, Patacchini R. alpha, beta-Unsaturated aldehydes contained in cigarette smoke elicit IL-8 release in pulmonary cells through mitogen-activated protein kinases. Am J Physiol Lung Cell Mol Physiol. 2009; 296: L839-L848.
31. Dal Negro, R.W., Wedzicha, J.A., Iversen, M., Fontana, G., Page, C., Cicero, A.F., Pozzi, E. and Calverley, P.M., 2017. Effect of erdosteine on the rate and duration of COPD exacerbations: the RESTORE study. Eur Respir J. 50: 1700711.
32. Rhee CK, Kang CM, You MB, et al. Effect of fudosteine on mucin production. Eur Respir J. 2008; 32: 1195-1202. doi: 10.1183/09031936.00018508.
33. Osoata GO, Hanazawa T, Brindicci C, et al. Peroxynitrite elevation in exhaled breath condensate of COPD and its inhibition by fudosteine. Chest. 2009; 135: 1513-1520. doi: 10.1378/chest.08-2105
34. Hodge S, Matthews G, Mukaro V, Ahern J, Shivam A, Hodge G, Holmes M, Jersmann H, Reynolds PN. Cigarette smoke-induced changes to alveolar macrophage phenotype and function are improved by treatment with procysteine. Am J Respir Cell Mol Biol. 2011; 44: 673-681. doi: 10.1165/rcmb.2009-0459OC.
35. Jaramillo MC, Zhang DD. The emerging role of the Nrf2-Keap1 signaling pathway in cancer. Genes Dev. 2013; 27: 2179-2191. doi: 10.1101/gad.225680.113.
36. Cui W, Zhang Z, Zhang P, Qu J, Zheng C, Mo X, Zhou W, Xu L, Yao H, Gao J. Nrf2 attenuates inflammatory response in COPD/emphysema: crosstalk with Wnt3a/beta-catenin and AMPK pathways. J Cell Mol Med. 2018; 22: 3514-3525. doi: 10.1111/jcmm.13628.
37. Kensler TW, Wakabayashi N, Biswal S. Cell survival responses to environmental stresses via the Keap1-Nrf2-ARE pathway. Annu Rev Pharmacol Toxicol. 2007; 47: 89-116. doi: 10.1146/annurev.pharmtox.46.120604.141046.
38. Zeng X, Liu X, Bao H. Sulforaphane suppresses lipopolysaccharide- and Pam3CysSerLys4-mediated inflammation in chronic obstructive pulmonary disease via toll-like receptors. FEBS Open Bio. 2021; 11(5):1313-1321. doi: 10.1002/2211-5463.13118.
39. Zeng X, Liu X, Bao H, Zhang Y, Wang X, Shi K, Pang Q. Effects of sulforaphane on Toll-like receptor 4/myeloid differentiation factor 88 pathway of monocyte-derived macrophages from patients with chronic obstructive pulmonary disease. CJTRD. 2014; 37(4): 250-254.
40. Harvey CJ, Thimmulappa RK, Sethi S, Kong X, Yarmus L, Brown RH, Feller-Kopman D, Wise R, Biswal S. Targeting Nrf2 signaling improves bacterial clearance by alveolar macrophages in patients with COPD and in a mouse model. Sci Transl Med. 2011; 3(78): 78ra32.
41. Yoon HY, Kang NI, Lee HK, Jang KY, Park JW, Park BH. Sulforaphane protects kidneys against ischemia-reperfusion injury through induction of the Nrf2-dependent phase 2 enzyme. Biochem Pharmacol. 2008; 75: 2214–2223. doi: 10.1016/j.bcp.2008.02.029.
42. Keum Y-S, Yu S, Chang PP-J, et al. Mechanism of action of sulforaphane: inhibition of p38 mitogen-activated protein kinase isoforms contributing to the induction of antioxidant response element–mediated heme oxygenase-1 in human hepatoma HepG2 cells. Cancer Res. 2006; 66: 8804-8813. doi: 10.1158/0008-5472.CAN-05-3513.

43. Mollazadeh H, Cicero AFG, Blesso CN, Pirro M, Majeed M, Sahebkar A. Immune modulation by curcumin: the role of interleukin-10. Crit Rev Food Sci Nutr. 2019; 59(1): 89-101.
44. Trujillo J, Chirino YI, Molina-Jijon E, Andérica-Romero AC, Tapia E, Pedraza-Chaverrí J. Renoprotective effect of the antioxidant curcumin: recent findings. Redox Biol. 2013; 1(1):448-456.
45. Safari S, Davoodi P, Soltani A, Fadavipour M, Rezaeian A, Heydari F, Khazeei Tabari MA, Akhlaghdoust M. Curcumin effects on chronic obstructive pulmonary disease: A systematic review. Health Sci Rep. 2023; 6(3): e1145. doi: 10.1002/hsr2.1145.
46. Suzuki M, Betsuyaku T, Ito Y, et al. Curcumin attenuates elastase- and cigarette smoke-induced pulmonary emphysema in mice. Am J Physiol Cell Mol Physiol. 2009; 296: L614-L623. doi: 10.1152/ajplung.90443.2008.
47. de Ligt M, Timmers S, Schrauwen P. Resveratrol and obesity: can resveratrol relieve metabolic disturbances? Biochim Biophys Acta 2015; 1852:1137-1144.
48. Bitterman JL, Chung JH. Metabolic effects of resveratrol: addressing the controversies. Cell Mol Life Sci 2015; 72:1473-1488.
49. Beijers RJHCG, Gosker HR, Schols AMWJ. Resveratrol for patients with chronic obstructive pulmonary disease: hype or hope? Curr Opin Clin Nutr Metab Care. 2018; 21(2): 138-144. doi: 10.1097/MCO.0000000000000444.
50. Chen J, Yang X, Zhang W, Peng D, Xia Y, Lu Y, Han X, Song G, Zhu J, Liu R.. Therapeutic effects of resveratrol in a mouse model of LPS and cigarette smoke-induced COPD. Inflammation 2016; 39:1949-1959.
51. Li S, Zhao G, Chen L, Ding Y, Lian J, Hong G, Lu Z. Resveratrol protects mice from paraquat-induced lung injury: the important role of sirt1 and nrf2 antioxidant pathways. Mol Med Rep 2016; 13:1833-1838.
52. Mokra D, Adamcakova J, Mokry J. Green Tea Polyphenol (-)-Epigallocatechin-3-Gallate (EGCG): A Time for a New Player in the Treatment of Respiratory Diseases? Antioxidants (Basel). 2022; 11(8): 1566. doi: 10.3390/antiox11081566
53. Yousefian M, Shakour N, Hosseinzadeh H, Hayes AW, Hadizadeh F, Karimi G. The natural phenolic compounds as modulators of NADPH oxidases in hypertension. Phytomedicine. 2019; 55: 200-213.
54. Liang Y, Liu KWK, Yeung SC, Li X, Ip MSM, Mak JCW. (-)-Epigallocatechin-3-gallate Reduces Cigarette Smoke-Induced Airway Neutrophilic Inflammation and Mucin Hypersecretion in Rats. Front Pharmacol. 2017; 8: 618. doi: 10.3389/fphar.2017.00618.
55. Shah ZA, Li RC, Ahmad AS, Kensler TW, Yamamoto M, Biswal S, Dore S. The flavanol (−)-Epicatechin prevents stroke damage through the Nrf2/HO1 pathway. J Cereb Blood Flow Metab. 2010; 30: 1951-1961. doi: 10.1038/jcbfm.2010.53.
56. Sussan TE, Rangasamy T, Blake DJ, Malhotra D, El-Haddad H, Bedja D, Yates MS, Kombairaju P, Yamamoto M, Liby KT, Sporn MB. Targeting Nrf2 with the triterpenoid CDDO- imidazolide attenuates cigarette smoke-induced emphysema and cardiac dysfunction in mice. Proc Natl Acad Sci. 2009; 106: 250-255. doi: 10.1073/pnas.0804333106
57. Hirota R, Nakamura H, Bhatti SA, Ngatu NR, Muzembo BA, Dumavibhat N, Eitoku M, Sawamura M, Suganuma N. Limonene inhalation reduces allergic airway inflammation in Dermatophagoides farinae-treated mice. Inhal. Toxicol. 2012; 24: 373-381. doi: 10.3109/08958378.2012.675528.
58. Zhu W, Liu X, Wang Y, Tong Y, Hu Y. Discovery of a novel series of α-terpineol derivatives as promising anti-asthmatic agents: Their design, synthesis, and biological evaluation. Eur J Med Chem. 2018; 143: 419-425. doi: 10.1016/j.ejmech.2017.07.068.
59. Chi T, Ji X, Xia M, Rong Y, Qiu F, Zou L. Effect of six extractions from Wuhu decoction on isolated tracheal smooth muscle in guinea pig. Zhong Guo Shi Yan Fang Ji Xue Za Zhi. 2009;15:52-55.
60. Kennedy-Feitosa E, Cattani-Cavalieri I, Barroso MV, Romana-Souza B, Brito-Gitirana L, Valenca SS. Eucalyptol promotes lung repair in mice following cigarette smoke-induced emphysema. Phytomedicine. 2019; 55: 70–79. doi:10.1016/j.phymed.2018.08.012
61. Xueshibojie L, Duo Y, Tiejun W. Taraxasterol Inhibits Cigarette Smoke-Induced Lung Inflammation by Inhibiting Reactive Oxygen Species-Induced TLR4 Trafficking to Lipid Rafts. Eur J Pharmacol. 2016; 789: 301-307. doi:10.1016/j.ejphar.2016.07.047.
62. Di Meo F, Lemaur V, Cornil J, Lazzaroni R, Duroux JL, Olivier Y, Trouillas P. Free radical scavenging by natural polyphenols: Atom versus electron transfer. J Phys Chem. A. 2013; 117: 2082–2092. doi: 10.1021/jp3116319.
63. Araujo NPDS, de Matos NA, Oliveira M, de Souza ABF, Castro TF, Machado-Júnior PA, de Souza DMS, Talvani A, Cangussú SD, de Menezes RCA, Bezerra FS. Quercetin Improves Pulmonary Function and Prevents Emphysema Caused by Exposure to Cigarette Smoke in Male Mice. Antioxidants (Basel). 2022; 11(2): 181. doi: 10.3390/antiox11020181
64. Lu J, Wang Z, Li S, Xin Q, Yuan M, Li H, Song X, Gao H, Pervaiz N, Sun X, Lv W. Quercetin Inhibits the Migration and Invasion of HCCLM3 Cells by Suppressing the Expression of p-Akt1, Matrix Metalloproteinase (MMP) MMP-2, and MMP-9. Med Sci Monit. 2018; 24: 2583–2589. doi: 10.12659/MSM.906172.
65. Kikuchi K, Uchikado H, Miyagi N, Morimoto Y, Ito T, Tancharoen S, Miura N, Miyata K, Sakamoto R, Kikuchi C, Iida N. Beyond neurological disease: New targets for edaravone (Review) Int J Mol Med. 2011; 28: 899-906.
66. Ito K, Ozasa H, Horikawa S. Edaravone protects against lung injury induced by intestinal ischemia/reperfusion in rat. Free Radic Biol Med. 2005; 38: 369-374. Clinical observation in edaravone treatment for acute cerebral infarction. Nigerian journal of clinical practice. 1324-7.

67. Sun Z, Xu Q, Gao G, Zhao M, Sun C. Clinical observation in edaravone treatment for acute cerebral infarction Niger. J Clin Pract. 2019; 22(10): 1324-1327, doi: 10.4103/njcp.njcp_367_18. Lee XR, Xiang GL. Effects of edaravone, the free radical scavenger, on outcomes in acute cerebral infarction patients treated with ultra-early thrombolysis of recombinant tissue plasminogen activator. Clinical Neurology and Neurosurgery. 2018 Apr 1;167:157-61.
68. Lee XR, Xiang GL. Xiang. Effects of edaravone, the free radical scavenger, on outcomes in acute cerebral infarction patients treated with ultra-early thrombolysis of recombinant tissue plasminogen activator. Clin Neurol Neurosurg, 2018; 167: 157-161, doi: 10.1016/j.clineuro.2018.02.026. Chen Y, Zhao Y. Curative efficacy of penehyclidine combined with edaravone on acute cerebral infarction and their effects on serum TNF-α and NDS score in rats. Eur Rev Med Pharmacol Sci. 2018 Jan 1;22(1):223-8.
69. Chen Y, Zhao Y. Zhao. Curative efficacy of penehyclidine combined with edaravone on acute cerebral infarction and their effects on serum TNF-α and NDS score in rats. Eur Rev Med Pharmacol Sci. 2018; 22(1): 223-228, doi: 10.26355/eurrev_201801_14121 Protective effects of edaravone combined puerarin on inhalation lung injury induced by black gunpowder smog. International Immunopharmacology. 2015 May 1;26(1):125-32.
70. Wang Z, Li R, Liu Y, Liu X, Chen W, Xu S, Guo Y, Duan J, Chen Y, Wang C. Protective effects of edaravone combined puerarin on inhalation lung injury induced by black gunpowder smog. Int. Immunopharmacol. 2015b; 26(1): 125-132, doi: 10.1016/j.intimp.2015.02.034
71. Miniati M, Cocci F, Monti S, Filippi E, Sarnelli R, Ferdeghini M, Gattai V, Pistolesi M. Lazaroid U-74389F attenuates phorbol ester-induced lung injury in rabbits. Eur Respir J. 1996; 9: 758-764.
72. Wang S, Lantz RC, Vermeulen MW, Chen GJ, Breceda V, Robledo RF, Hays AM, Young S, Witten ML. Functional alterations of alveolar macrophages subjected to smoke exposure and antioxidant lazaroids. Toxicology and industrial health. 1999; 15(5): 464-469.
73. Muscoli C, Sacco I, Alecce W, Palma E, Nistico R, Costa N, Clementi F, Rotiroti D, Romeo F, Salvemini D, Mehta JL. The protective effect of superoxide dismutase mimetic M40401 on balloon injury-related neointima formation: role of the lectin-like oxidized low-density lipoprotein receptor-1. J Pharmacol Exp Ther. 2004; 311: 44-50. doi: 10.1124/jpet.104.068205
74. Smith KR. Uyeminami DL, Kodavanti UP, Crapo JD, Chang LY, Pinkerton KE. Inhibition of tobacco smoke-induced lung inflammation by a catalytic antioxidant. Free Radic Biol Med. 2002; 33: 1106–1114. doi: 10.1016/S0891-5849(02)01003-1.
75. Yao H, Arunachalam G, Hwang JW, Chung S, Sundar IK, Kinnula VL, Crapo JD, Rahman I. Extracellular superoxide dismutase protects against pulmonary emphysema by attenuating oxidative fragmentation of ECM. Proc Natl Acad Sci. 2010; 107: 15571-15576. doi: 10.1073/pnas.1007625107.
76. Tollefson AK, Oberley-Deegan RE, Butterfield KT, Nicks ME, Weaver MR, Remigio LK, Decsesznak J, Chu HW, Bratton DL, Riches DW, Bowler RP. Endogenous enzymes (NOX and ECSOD) regulate smoke-induced oxidative stress. Free Radic Biol Med. 2010; 49: 1937-1946. doi: 10.1016/j.freeradbiomed.2010.09.022.
77. Xu J, Li T, Wu H, Xu T. Role of thioredoxin in lung disease. Pulm Pharmacol Ther. 2012; 25(2): 154-162. doi: 10.1016/j.pupt.2012.01.002.
78. Li Y, Liu W, Xing G, Tian C, Zhu Y, He F. Direct association of hepatopoietin with thioredoxin constitutes a redox signal transduction in activation of AP-1/NF-kappaB. Cell Signal. 2005; 17: 985-996.
79. Souza DG, Vieira AT, Pinho V, Sousa LP, Andrade AA, Bonjardim CA, McMillan M, Kahn M, Teixeira MM. NF-kappaB plays a major role during the systemic and local acute inflammatory response following intestinal reperfusion injury. Br J Pharmacol. 2005; 145: 246-254.
80. Tanabe N, Hoshino Y, Marumo S, Kiyokawa H, Sato S, Kinose D, Uno K, Muro S, Hirai T, Yodoi J, Mishima M. Thioredoxin-1 protects against neutrophilic inflammation and emphysema progression in a mouse model of chronic obstructive pulmonary disease exacerbation. PLoS One. 2013; 8(11): e79016. doi: 10.1371/journal.pone.0079016.
81. Takimoto T, Yoshida M, Hirata H, Kashiwa Y, Takeda Y, Goya S, Kijima T, Kumagai T, Tachibana I, Kawase I. 4-Hydroxy-2-nonenal induces chronic obstructive pulmonary disease-like histopathologic changes in mice. Biochem Biophys Res Commun. 2012; 420(1): 84-90.
82. Fang J, Holmgren A. Inhibition of thioredoxin and thioredoxin reductase by 4-hydroxy-2-nonenal in vitro and in vivo. J Am Chem Soc. 2006; 128(6): 1879-1885.
83. Liu J, Huang J, Liu H, Chen C, Xu J, Zhong L. Elevated serum 4HNE plus decreased serum thioredoxin: Unique feature and implications for acute exacerbation of chronic obstructive pulmonary disease. PLoS ONE. 2021; 16(1): e0245810. doi: 10.1371/journal.pone.0245810.
84. Shi H, Timmins G, Monske M, Burdick A, Kalyanaraman B, Liu Y, Clement JL, Burchiel S, Liu KJ. Evaluation of spin trapping agents and trapping conditions for detection of cell-generated reactive oxygen species. Arch Biochem Biophys. 2005; 437: 59-68.
85. Chabrier PE, Auguet M, Spinnewyn B, Auvin S, Cornet S, Demerlé-Pallardy C, Guilmard-Favre C, Marin JG, Pignol B, Gillard-Roubert V, Roussillot-Charnet C. BN 80933, a dual inhibitor of neuronal nitric oxide synthase and lipid peroxidation: a promising neuroprotective strategy. Proc Natl Acad Sci U S A. 1999; 96:10824-10829. doi: 10.1073/pnas.96.19.10824.

86. Valenca SS, Rueff-Barroso CR, Pimenta WA, Melo AC, Nesi RT, Silva MA, Porto LC. L-NAME and L-arginine differentially ameliorate cigarette smoke-induced emphysema in mice. Pulm Pharmacol Ther. 2011; 24: 587-594.
87. Kuzmov A, Minko T. Nanotechnology approaches for inhalation treatment of lung diseases. J Control Release. 2015; 219: 500-518. doi: 10.1016/j.jconrel.2015.07.024
88. Rohilla S, Harish Dureja. Effect of Chitosan Coating on the Physiochemical Characteristics of Gefitinib Loaded Nanoliposomes. Int J Pharm Sci Res. 2018; 9(12): 1000-1013.
89. Levchenko TS, Hartner WC, Torchilin VP. Liposomes in diagnosis and treatment of cardiovascular disorders. Methodist Debakey Cardiovasc J. 2012; 8: 36-41. doi: 10.14797/mdcj-8-1-36
90. Rohilla S, Harish Dureja. Recent Patents, Formulation and Characterization of Nanoliposomes. Recent Pat Drug Deliv Formul. 2015; 9(3): 213-224
91. Rohilla S, Rajendra Awasthi, Meenu Mehta, Dinesh Kumar Chellappan, Gaurav Gupta, Monica Gulati, Sachin Kumar Singh, Krishnan Anand, Brian G. Oliver, Kamal Dua, Harish Dureja. Preparation and Evaluation of Gefitinib Containing Nanoliposomal Formulation for Lung Cancer Therapy. BioNanoScience 2022; 12: 241-255. doi: 10.1007/s12668-022-00938-6.
92. Willis L, Hayes D, Mansour HM. Therapeutic liposomal dry powder inhalation aerosols for targeted lung delivery. Lung. 2012; 190: 251-262. doi: 10.1007/s00408-011-9360-x.
93. Manconi M, Manca ML, Valenti D, Escribano E, Hillaireau H, Fadda AM, Fattal E. Chitosan and hyaluronan coated liposomes for pulmonary administration of curcumin. Int J Pharm. 2017; 525: 203-210.
94. Garbuzenko OB, Mainelis G, Taratula O, Minko T. Inhalation treatment of lung cancer: the influence of composition, size and shape of nanocarriers on their lung accumulation and retention. Cancer Biol Med. 2014; 11: 44-55. doi: 10.7497/j.issn.2095-3941.2014.01.004
95. Li N, Weng D, Wang SM, Zhang Y, Chen SS, Yin ZF, Zhai J, Scoble J, Williams CC, Chen T, Qiu H. Surfactant protein-A nanobody-conjugated liposomes loaded with methylprednisolone increase lung-targeting specificity and therapeutic effect for acute lung injury. Drug Deliv. 2017; 24: 1770-1781. doi: 10.1080/10717544.2017.1402217
96. Cipolla D, Blanchard J, Gonda I. Development of liposomal ciprofloxacin to treat lung infections. Pharmaceutics. 2016; 8: 6. doi: 10.3390/pharmaceutics8010006
97. De Leo V, Ruscigno S, Trapani A, Di Gioia S, Milano F, Mandracchia D, Comparelli R, Castellani S, Agostiano A, Trapani G, Catucci L, Conese M. Preparation of drug-loaded small unilamellar liposomes and evaluation of their potential for the treatment of chronic respiratory diseases. Int J Pharm. 2018; 545(1-2): 378-388. doi: 10.1016/j.ijpharm.2018.04.030
98. Rohilla S, Rohilla A, Narwal S, Dureja H, Bhagwat DP. Global Trends of Cosmeceutical in Nanotechnology: A Review. Pharm Nanotechnol. 2023.
99. Villegas L, Stidham T, Nozik-Grayck E. Oxidative Stress and Therapeutic Development in Lung Diseases. J Pulm Respir Med. 2014; 4: 99.
100. Meenach SA, Anderson KW, Hilt JZ, McGarry RC, Mansour HM. High-performing dry powder inhalers of paclitaxel DPPC/DPPG lung surfactant-mimic multifunctional particles in lung cancer: physicochemical characterization, in vitro aerosol dispersion, and cellular studies. AAPS Pharm Sci Tech. 2014; 15: 1574-1587. doi: 10.1208/s12249-014-0182-z.
101. Castellani S, Trapani A, Spagnoletta A, di Toma L, Magrone T, Di Gioia S, Mandracchia D, Trapani G, Jirillo E, Conese M. Nanoparticle delivery of grape seed-derived proanthocyanidins to airway epithelial cells dampens oxidative stress and inflammation. J Transl Med. 2018; 16(1): 140. doi: 10.1186/s12967-018-1509-4.
102. Thanki K, Zeng X, Justesen S, Tejlmann S, Falkenberg E, Van Driessche E, Mørck Nielsen H, Franzyk H, Foged C. Engineering of small interfering RNA-loaded lipidoid-poly(DL-lactic-co-glycolic acid) hybrid nanoparticles for highly efficient and safe gene silencing: A quality by design-based approach. Eur J Pharm Biopharm. 2017; 120: 22-33. doi: 10.1016/j.ejpb.2017.07.014.
103. Akinc A, Zumbuehl A, Goldberg M, Leshchiner ES, Busini V, Hossain N, Bacallado SA, Nguyen DN, Fuller J, Alvarez R, Borodovsky A, Borland T, Constien R, de Fougerolles A, Dorkin JR, Narayanannair Jayaprakash K, Jayaraman M, John M, Koteliansky V, Manoharan M, Nechev L, Qin J, Racie T, Raitcheva D, Rajeev KG, Sah DW, Soutschek J, Toudjarska I, Vornlocher HP, Zimmermann TS, Langer R, Anderson DG. A combinatorial library of lipid-like materials for delivery of RNAi therapeutics. Nat Biotechnol. 2008; 26(5): 561-569. doi: 10.1038/nbt1402.
104. Wang Y, Kho K, Cheow WS, Hadinoto K. A comparison between spray drying and spray freeze drying for dry powder inhaler formulation of drug-loaded lipid–polymer hybrid nanoparticles. Int J Pharm. 2012; 424: 98-106. doi: 10.1016/j.ijpharm.2011.12.045.
105. Chikuma K, Arima K, Asaba Y, Kubota R, Asayama S, Sato K, Kawakami H. The potential of lipid-polymer nanoparticles as epigenetic and ROS control approaches for COPD. Free Radic Res. 2020; 54(11-12): 829-840. doi: 10.1080/10715762.2019.1696965.
106. Ourique AF, Chaves Pdos S, Souto GD, Pohlmann AR, Guterres SS, Beck RC. Redispersible liposomal-N-acetylcysteine powder for pulmonary administration: development, in vitro characterization and antioxidant activity. Eur J Pharm Sci. 2014; 65: 174-182. doi: 10.1016/j.ejps.2014.09.017.
107. Wigenstam E, Rocksen D, Ekstrand-Hammarstrom B, Bucht A. Treatment with dexamethasone or liposome-encapsuled vitamin E provides beneficial effects after chemical-induced lung injury. Inhal Toxicol. 2009; 21(11): 958-964. doi: 10.1080/08958370802596298.

108. Conti DS, Brewer D, Grashik J, Avasarala S, da Rocha SR. Poly(amidoamine) dendrimer nanocarriers and their aerosol formulations for siRNA delivery to the lung epithelium. Mol Pharm. 2014; 11(6): 1808-1822. doi: 10.1021/mp4006358.
109. Bohr A, Tsapis N, Foged C, Andreana I, Yang M, Fattal E. Treatment of acute lung inflammation by pulmonary delivery of anti-TNF-α siRNA with PAMAM dendrimers in a murine model. Eur J Pharm Biopharm. 2020; 156: 114-120. doi: 10.1016/j.ejpb.2020.08.009.
110. Castellani S, Trapani A, Spagnoletta A, di Toma L, Magrone T, Di Gioia S, Mandracchia D, Trapani G, Jirillo E, Conese M. Nanoparticle delivery of grape seed-derived proanthocyanidins to airway epithelial cells dampens oxidative stress and inflammation. J Transl Med. 2018; 16(1): 140. doi: 10.1186/s12967-018-1509-4.
111. Carvalho FO, Silva ER, Nunes PS, Felipe FA, Ramos KPP, Ferreira LAS, Lima VNB, Shanmugam S, Oliveira AS, Guterres SS, Camargo EA, Cravalho Olivera TV, de Albuquerque Júnior RLC, de Lucca Junior W, Quintans-Júnior LJ, Araújo AAS. Effects of the solid lipid nanoparticle of carvacrol on rodents with lung injury from smoke inhalation. Naunyn Schmiedebergs Arch Pharmacol. 2020; 393(3): 445-455. doi: 10.1007/s00210-019-01731-1.
112. Jeong D, Kang C, Jung E, Yoo D, Wu D, Lee D. Porous antioxidant polymer microparticles as therapeutic systems for the airway inflammatory diseases. J Control Release. 2016; 233: 72-80. doi: 10.1016/j.jconrel.2016.04.039.
113. Yoo D, Guk K, Kim H, Khang G, Wu D, Lee D. Antioxidant polymeric nanoparticles as novel therapeutics for airway inflammatory diseases. Int J Pharm. 2013; 450(1-2): 87-94. doi: 10.1016/j.ijpharm.2013.04.028.
114. Craparo EF, Ferraro M, Pace E, Bondì ML, Giammona G, Cavallaro G. Polyaspartamide-Based Nanoparticles Loaded with Fluticasone Propionate and the In Vitro Evaluation towards Cigarette Smoke Effects. Nanomaterials (Basel). 2017; 7(8): 222. doi: 10.3390/nano7080222.
115. Lee WH, Loo CY, Young PM, Rohanizadeh R, Traini D. Curcumin Nanoparticles Attenuate Production of Pro-inflammatory Markers in Lipopolysaccharide-Induced Macrophages. Pharm Res. 2016; 33(2): 315-327. doi: 10.1007/s11095-015-1789-9.
116. Mohamed A, Pekoz AY, Ross K, Hutcheon GA, Saleem IY. Pulmonary delivery of Nanocomposite Microparticles (NCMPs) incorporating miR-146a for treatment of COPD. Int J Pharm. 2019; 569: 118524. doi: 10.1016/j.ijpharm.2019.118524.
117. Frede A, Neuhaus B, Knuschke T, Wadwa M, Kollenda S, Klopfleisch R, Hansen W, Buer J, Bruder D, Epple M, Westendorf AM. Local delivery of siRNA-loaded calcium phosphate nanoparticles abates pulmonary inflammation. Nanomedicine. 2017; 13(8): 2395-2403. doi: 10.1016/j.nano.2017.08.001.
118. Passi M, Kumar V, Packirisamy G. Theranostic nanozyme: Silk fibroin based multifunctional nanocomposites to combat oxidative stress. Mater Sci Eng C. 2020; 107: 110255.
119. Raula J, Rahikkala A, Halkola T, Pessi J, Peltonen L, Hirvonen J, Järvinen K, Laaksonen T, Kauppinen EI. Coated particle assemblies for the concomitant pulmonary administration of budesonide and salbutamol sulphate. Int J Pharm. 2013; 441(1-2): 248-54. doi: 10.1016/j.ijpharm.2012.11.036.
120. Geiser M, Quaile O, Wenk A, Wigge C, Eigeldinger-Berthou S, Hirn S, Schäffler M, Schleh C, Möller W, Mall MA, Kreyling WG. Cellular uptake and localization of inhaled gold nanoparticles in lungs of mice with chronic obstructive pulmonary disease. Part Fibre Toxicol. 2013; 10: 19. doi: 10.1186/1743-8977-10-19.
121. Hood ED, Chorny M, Greineder CF, S Alferiev I, Levy RJ, Muzykantov VR. Endothelial targeting of nanocarriers loaded with antioxidant enzymes for protection against vascular oxidative stress and inflammation. Biomaterials. 2014; 35(11): 3708-3715. doi: 10.1016/j.biomaterials.2014.01.023.
122. Gil D, Rodriguez J, Ward B, Vertegel A, Ivanov V, Reukov V. Antioxidant Activity of SOD and Catalase Conjugated with Nanocrystalline Ceria. Bioengineering (Basel). 2017 Feb 25;4(1):18. doi: 10.3390/bioengineering4010018.
123. Li X, Yang H, Wu S, Meng Q, Sun H, Lu R, Cui J, Zheng Y, Chen W, Zhang R, Aschner M, Chen R. Suppression of PTPN6 exacerbates aluminum oxide nanoparticle-induced COPD-like lesions in mice through activation of STAT pathway. Part Fibre Toxicol. 2017; 14(1): 53. doi: 10.1186/s12989-017-0234-0.
124. Ding Y, Jiang Z, Saha K, Kim CS, Kim ST, Landis RF, Rotello VM. Gold nanoparticles for nucleic acid delivery. Mol Ther. 2014; 22(6): 1075-1083. doi: 10.1038/mt.2014.30.
125. Gil D, Rodriguez J, Ward B, Vertegel A, Ivanov V, Reukov V. Antioxidant Activity of SOD and Catalase Conjugated with Nanocrystalline Ceria. Bioengineering (Basel). 2017; 4(1): 18. doi: 10.3390/bioengineering4010018.
126. Fytianos K, Chortarea S, Rodriguez-Lorenzo L, Blank F, von Garnier C, Petri-Fink A, Rothen-Rutishauser B. Aerosol Delivery of Functionalized Gold Nanoparticles Target and Activate Dendritic Cells in a 3D Lung Cellular Model. ACS Nano. 2017; 11(1): 375-383. doi: 10.1021/acsnano.6b06061.
127. Bhushan B, Gopinath P. Antioxidant nanozyme: a facile synthesis and evaluation of the reactive oxygen species scavenging potential of nanoceria encapsulated albumin nanoparticles. J Mater Chem. 2015; B3: 4843-4852. doi: 10.1039/C5TB00572H
128. Muralidharan P, Hayes D, Black SM, Mansour HM. Microparticulate/nanoparticulate powders of a novel Nrf2 activator and an aerosol performance enhancer for pulmonary delivery targeting the lung Nrf2/Keap-1 pathway. Mol Syst Des Eng. 2016; 1: 48-65. doi: 10.1039/C5ME00004A

129. Ni S, Liu Y, Tang Y, Chen J, Li S, Pu J, Han L. GABAB receptor ligand-directed trimethyl chitosan/tripolyphosphate nanoparticles and their pMDI formulation for survivin siRNA pulmonary delivery. Carbohydr Polym. 2018; 179: 135-144. doi: 10.1016/j.carbpol.2017.09.075.
130. Vij N. Nano-based theranostics for chronic obstructive lung diseases: challenges and therapeutic potential. Expert Opin Drug Deliv. 2011; 8: 1105-1109. doi: 10.1517/17425247.2011.597381
131. Kim S, Park H, Song Y, Hong D, Kim O, Jo E, Khang G, Lee D. Reduction of oxidative stress by p-hydroxybenzyl alcohol-containing biodegradable polyoxalate nanoparticulate antioxidant. Biomaterials. 2011 Apr;32(11):3021-9. doi: 10.1016/j.biomaterials.2010.11.033.
132. Dailey LA, Kissel T. New poly(lactic-co-glycolic acid) derivatives: Modular polymers with tailored properties. Drug Discov Today Tech. 2005; 2: 7-13.
133. Ryan GM, Kaminskas LM, Kelly BD, Owen DJ, McIntosh MP, Porter CJ. Pulmonary administration of PEGylated polylysine dendrimers: absorption from the lung versus retention within the lung is highly size-dependent. Mol Pharm. 2013; 10(8): 2986-95. doi: 10.1021/mp400091n.
134. Kaminskas LM, McLeod VM, Ryan GM, Kelly BD, Haynes JM, Williamson M, Thienthong N, Owen DJ, Porter CJ. Pulmonary administration of a doxorubicin-conjugated dendrimer enhances drug exposure to lung metastases and improves cancer therapy. J Control Release. 2014; 183: 18-26. doi: 10.1016/j.jconrel.2014.03.012.
135. Zhong Q, Merkel OM, Reineke JJ, da Rocha SR. Effect of the Route of Administration and PEGylation of Poly(amidoamine) Dendrimers on Their Systemic and Lung Cellular Biodistribution. Mol Pharm. 2016; 13(6): 1866-1878. doi: 10.1021/acs.molpharmaceut.6b00036.
136. Khan OF, Zaia EW, Jhunjhunwala S, Xue W, Cai W, Yun DS, Barnes CM, Dahlman JE, Dong Y, Pelet JM, Webber MJ, Tsosie JK, Jacks TE, Langer R, Anderson DG. Dendrimer-Inspired Nanomaterials for the in Vivo Delivery of siRNA to Lung Vasculature. Nano Lett. 2015; 15(5): 3008-3016. doi: 10.1021/nl5048972.
137. Bohr A, Tsapis N, Andreana I, Chamarat A, Foged C, Delomenie C, Noiray M, El Brahmi N, Majoral JP, Mignani S, Fattal E. Anti-Inflammatory Effect of Anti-TNF-α SiRNA Cationic Phosphorus Dendrimer Nanocomplexes Administered Intranasally in a Murine Acute Lung Injury Model. Biomacromolecules. 2017; 18(8): 2379-2388. doi: 10.1021/acs.biomac.7b00572.
138. Pitard B, Bello-Roufaï M, Lambert O, Richard P, Desigaux L, Fernandes S, Lanctin C, Pollard H, Zeghal M, Rescan PY, Escande D. Negatively charged self-assembling DNA/poloxamine nanospheres for in vivo gene transfer. Nucleic Acids Res. 2004; 32(20): e159. doi: 10.1093/nar/gnh153.
139. Jiang J, Liu Y, Wu C, Qiu Y, Xu X, Lv H, Bai A, Liu X. Development of drug-loaded chitosan hollow nanoparticles for delivery of paclitaxel to human lung cancer A549 cells. Drug Dev Ind Pharm. 2017; 43(8): 1304-1313. doi: 10.1080/03639045.2017.1318895.
140. Al-Jamal WT, Kostarelos K. Liposomes: from a clinically established drug delivery system to a nanoparticle platform for theranostic nanomedicine. Acc Chem Res. 2011; 44: 1094-1104. doi: 10.1021/ar200105p
141. Monument MJ, Hart DA, Befus AD, Salo PT, Zhang M, Hildebrand KA. The mast cell stabilizer ketotifen reduces joint capsule fibrosis in a rabbit model of post-traumatic joint contractures. Inflamm Res. 2012; 61(4): 285-292. doi: 10.1007/s00011-011-0409-3.
142. Xu Y, Liu H, Song L. Novel drug delivery systems targeting oxidative stress in chronic obstructive pulmonary disease: a review. J Nanobiotechnol. 2020; 18: 145. doi:10.1186/s12951-020-00703-5
143. Lin YW, Wong J, Qu L, Chan HK, Zhou QT. Powder Production and Particle Engineering for Dry Powder Inhaler Formulations. Curr Pharm Des. 2015; 21(27): 3902-3916. doi: 10.2174/1381612821666150820111134.
144. Zhang L, Zhang X, Li J, Beck-Broichsitter M, Muenster U, Wang X, Zhao J, Mao S. Optimization of budesonide-loaded large-porous microparticles for inhalation using quality by design approach. J Drug Deliv Sci Technol. 2019; 53: 101140. doi:10.1016/j.jddst.2019.101140.
145. Zellnitz S, Zellnitz L, Müller MT, Meindl C, Schröttner H, Fröhlich E. Impact of drug particle shape on permeability and cellular uptake in the lung. Eur J Pharm Sci. 2019 Nov 1;139:105065. doi: 10.1016/j.ejps.2019.105065.
146. Fallacara A, Busato L, Pozzoli M, Ghadiri M, Ong HX, Young PM, Manfredini S, Traini D. Co-Spray-Dried Urea Cross-Linked Hyaluronic Acid and Sodium Ascorbyl Phosphate as Novel Inhalable Dry Powder Formulation. J Pharm Sci. 2019; 108(9): 2964-2971. doi: 10.1016/j.xphs.2019.04.015.
147. Muralidharan P, Hayes D Jr, Black SM, Mansour HM. Microparticulate/Nanoparticulate Powders of a Novel Nrf2 Activator and an Aerosol Performance Enhancer for Pulmonary Delivery Targeting the Lung Nrf2/Keap-1 Pathway. Mol Syst Des Eng. 2016; 1(1): 48-65. doi: 10.1039/C5ME00004A.
148. Moura CU, Neves F, Costa E. Impact of jet-milling and wet-polishing size reduction technologies on inhalation API particle properties. Powder Technol. 2016; 298: 90-98.
149. Beijers RJHCG, Gosker HR, Schols AMWJ. Resveratrol for patients with chronic obstructive pulmonary disease: hype or hope? Curr Opin Clin Nutr Metab Care. 2018 Mar;21(2):138-144. doi: 10.1097/MCO.0000000000000444.
150. Dumont EF, Oliver AJ, Ioannou C, Billiard J, Dennison J, van den Berg F, Yang S, Chandrasekaran V, Young GC, Lahiry A, Starbuck DC, Harrell AW, Georgiou A, Hopchet N, Gillies A, Baker SJ. A Novel Inhaled Dry-Powder Formulation of Ribavirin Allows for Efficient Lung Delivery in Healthy Participants and Those with Chronic Obstructive Pulmonary Disease in a Phase 1 Study. Antimicrob Agents Chemother. 2020; 64(5): e02267-19. doi: 10.1128/AAC.02267-19.

151. Amore E, Manca ML, Ferraro M, Valenti D, La Parola V, Di Vincenzo S, Gjomarkaj M, Giammona G, Bondì ML, Pace E. Salmeterol Xinafoate (SX) loaded into mucoadhesive solid lipid microparticles for COPD treatment. Int J Pharm. 2019; 562: 351-358. doi: 10.1016/j.ijpharm.2019.03.059.
152. Amore E, Ferraro M, Manca ML, Gjomarkaj M, Giammona G, Pace E, Bondì ML. Mucoadhesive solid lipid microparticles for controlled release of a corticosteroid in the chronic obstructive pulmonary disease treatment. Nanomedicine (Lond). 2017; 12(19): 2287-2302. doi: 10.2217/nnm-2017-0072.
153. Simková K, Joost B, Imanidis G. Production of fast-dissolving low-density powders for improved lung deposition by spray drying of a nanosuspension. Eur J Pharm Biopharm. 2020; 146: 19-31. doi: 10.1016/j.ejpb.2019.11.003.
154. Mohamed A, Pekoz AY, Ross K, Hutcheon GA, Saleem IY. Pulmonary delivery of Nanocomposite Microparticles (NCMPs) incorporating miR-146a for treatment of COPD. Int J Pharm. 2019; 569: 118524. doi: 10.1016/j.ijpharm.2019.118524.
155. Dormenval C, Lokras A, Cano-Garcia G, Wadhwa A, Thanki K, Rose F, Thakur A, Franzyk H, Foged C. Identification of Factors of Importance for Spray Drying of Small Interfering RNA-Loaded Lipidoid-Polymer Hybrid Nanoparticles for Inhalation. Pharm Res. 2019; 36(10): 142. doi: 10.1007/s11095-019-2663-y.
156. Papay ZE, Kósa A, Böddi B, Merchant Z, Saleem IY, Zariwala MG, Klebovich I, Somavarapu S, Antal I. Study on the Pulmonary Delivery System of Apigenin-Loaded Albumin Nanocarriers with Antioxidant Activity. J Aerosol Med Pulm Drug Deliv. 2017; 30(4): 274-288. doi: 10.1089/jamp.2016.1316.
157. Li BS, Zhu RZ, Lim SH, Seo JH, Choi BM. Apigenin Alleviates Oxidative Stress-Induced Cellular Senescence via Modulation of the SIRT1-NAD-CD38 Axis. Am J Chin Med. 2021; 49(5):1235-1250. doi: 10.1142/S0192415X21500592.
158. Mueller C, Flotte TR. Gene therapy for cystic fibrosis. Clin Rev Allergy Immunol. 2008;35:164–178. doi:10.1007/s12016-008-8080-3
159. Swaminathan J, Ehrhardt C. Liposomal delivery of proteins and peptides. Expert Opin Drug Deliv. 2012;9:1489–1503. doi:10.1517/17425247.2012.735658
160. Al-Jamal R, Wallace W, Harrison D. Gene therapy for chronic obstructive pulmonary disease: twilight or triumph? Expert Opin Biol Ther. 2005; 5: 333–346. doi:10.1517/14712598.5.3.333
161. Zhao Y, Xu A, Xu Q, Zhao W, Li D, Fang X, Ren Y. Bone marrow mesenchymal stem cell transplantation for treatment of emphysemic rats. Int J Clin Exp Med. 2014; 7(4): 968-972.
162. Rojas M, Xu J, Woods CR, Mora AL, Spears W, Roman J, Brigham KL. Bone marrow-derived mesenchymal stem cells in repair of the injured lung. Am J Respir Cell Mol Biol. 2005; 33(2): 145-152. doi: 10.1165/rcmb.2004-0330OC.